Left Ventricular Long Axis Dynamics in Pathological and Physiological Left Ventricular Hypertrophy.

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ABSTRACT

Sub - endocardial fibres line the inner surface of both ventricles and are responsible for longitudinal oscillations of the mitral annulus, such oscillations may be measured using tissue Doppler echocardiography (TDE). During systole the annulus descends and during early diastole (E_{TDE}) and atrial systole (A_{TDE}) it ascends. This thesis examined whether changes in the velocity of the annulus in each of these phases of oscillation, measured using tissue Doppler echocardiography (TDE), could determine the nature of increases in left ventricular size (pathological or physiological). **Study one** examined differences at rest in longitudinal velocities between individuals with hypertrophic cardiomyopathy (HCM), hypertension (HT), weightlifters, runners and controls, (n = 15 all groups) and all groups were aged between 20 - 36 years. The results demonstrated that both pathological groups had systolic and E_{TDE} velocities significantly lower than groups with physiological hypertrophy (weightlifters or runners) or controls $p < 0.05$. A_{TDE} however was not significantly different between groups. Additionally runners also demonstrated a significantly higher E_{TDE} than either weightlifters or controls ($p < 0.05$). Binomial logistic regression identified longitudinal systolic velocity < 9 cm s^{-1} and E_{TDE} velocity < 11 cm s^{-1} as the best combination of variables to predict pathological increases in heart size. **Study two** examined older subjects in order to determine whether the criteria set out in study one were applicable to senior athletes. The subject groups were the same as in study one however all subjects were aged between 36 - 55. In this case systolic annular velocity was significantly lower in groups with pathological LVH but E_{TDE} < 9 cm s^{-1} was a better differentiator. Binomial logistic regression identified E_{TDE} < 9 cm s^{-1} and a mitral E / A ratio < 1 as the best combination of variables to predict pathological LVH. **Study three** examined the age related changes in long axis function using the pooled data from studies one and two. This demonstrated that in the pathological LVH groups only E_{TDE} / A_{TDE} ratio was significantly correlated with age ($r = -0.5$ $p < 0.05$) suggesting that there appears to be no summation of the effects of pathology and age on mitral annular velocities. The control groups demonstrated a significant age related reduction in all long axis variables (systolic velocity $r = -0.7$ $p < 0.05$; E_{TDE} $r = -0.6$ $p < 0.01$; A_{TDE} $r = 0.5$ $p < 0.05$; E_{TDE} / A_{TDE} $r = -0.5$ $p < 0.01$). Weightlifters however did not demonstrate an age related decline in either systolic or diastolic annular velocities. Runners had no age related decline in systolic annular velocities, and whilst they had an age dependent fall in E_{TDE} ($r = -0.62$ $p < 0.05$) the older runners E_{TDE} were still significantly faster ($p < 0.05$) than that seen in control subjects. **Study four** investigated relationship between mitral annular velocity and $\dot{V}O_{2PEAK}$ in runners, weightlifters and controls. These results demonstrated peak exercise E_{TDE} strongly correlated to $\dot{V}O_{2PEAK}$ ($r = 0.8$ $p < 0.01$). **Conclusions.** Taken together these data suggest that longitudinal velocities of the mitral annulus may be useful in determining the nature of increases in heart size, in addition the increased performance of endurance - trained athletes is due in part to functional changes of the long axis.

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CERTIFICATE OF RESEARCH.

This is to certify that the work described in this thesis is the result of my own work. This research programme was carried out in collaboration with the University Hospital of Wales Department of Cardiology.
Neither this thesis nor any part of it has been presented or is currently submitted in candidature for any degree at any other University.

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GLOSSARY

HT. Hypertensive.

HCM. Hypertrophic cardiomyopathy.

DCM. Dilated Cardiomyopathy.

IVCP. Iso - Volumic Contraction Phase.

CAD. Coronary Artery Disease.

EDD. *End Diastolic Diameter.* The diameter across the short axis of the ventricle at the end of diastole.

IVS. *Inter ventricular Septum* Thickness of the inter ventricular septum measured at the end of diastole.

ESD. *End Systolic Dimension.* The diameter across the short axis of the ventricle at the end of systole.

EF. *Ejection Fraction.* The percentage of blood ejected from the left ventricle during systole compared to the total amount in the ventricle at end diastole.

LVM. *Left Ventricular Mass.* The estimated mass of the left ventricle from echocardiographic measurements.

LVMi. *Left Ventricular Mass Index.* LVM divided by body surface area (BSA).

Mitral E. The peak velocity of blood flowing through the mitral valve during early (E) diastole.

Mitral A. The peak velocity of blood flowing through the mitral valve during atrial systole (A).

Doppler. An echocardiographic technique used to measure the velocity of blood flow.

TDE. Tissue Doppler Echocardiography. An echocardiographic technique used to measure the velocity of contracting tissue.

Annular Systolic Descent. The velocity of the mitral annulus as it descends during ventricular systole.

E_{TDE}. The velocity of the mitral annulus as it ascends during early diastole.

A_{TDE}. The velocity of the mitral annulus as it ascends during atrial systole.

PCWP. Pulmonary capillary wedge pressure.

OUTLINE OF THESIS

The thesis is organised into 7 chapters.

Chapter 1 – Introduction

Chapter 2 – The Review of Literature.

The literature review details the underlying mechanism of long axis displacement of the mitral valve, look at how the velocity of mitral valve movement can be measured, and examine some of the previous work using long axis movement of the mitral valve in a variety of pathologies.

Chapter 3 – Study 1.

This study examined the differences in long axis movement in patients with increased cardiac mass due to hypertrophic cardiomyopathy and systemic hypertension and compared them to athletes from different disciplines (endurance and strength) as well as to controls.

Chapter 4 - Study 2.

Study 2 examined differences in long axis movement between patients with pathological increases in cardiac mass and athletes and controls. Specifically this

study looked at older subjects to determine whether conclusions from study 1 were valid for older subjects.

Chapter 5 - Comparison Study.

Building on previous work, this involved a comparison between the findings of study 1 and 2 to determine age related changes in the long axis mitral valve movement.

Chapter 6 - Study 4.

The final study examined the effects of an acute bout of exercise on the mitral valve movement in athletes and controls, in order to determine if differences seen at rest are evident at peak exercise.

Chapter 7 – Summary of Results.

Presents an overview of the main findings of the thesis. Furthermore specific acceptance or rejection of hypotheses will be stated. Future directions for further research will also be developed.

CHAPTER 1: INTRODUCTION

1.1 INTRODUCTION

The ability of a variety of athletic endeavours to produce changes in the geometry and mass of the left ventricle of the human heart is well established (Morganroth *et al.*, 1975; Foster *et al.*, 1986; Pellicia *et al.*, 1991; George *et al.*, 1991; Bryan *et al.*, 1992; Richey & Brown 1998; Pluim *et al.*, 2000) this condition is generally referred to as 'athletes heart'. In fact, a century ago Henschen *et al.*, (1899) demonstrated cardiac enlargement in cross country skiers and even demonstrated good correlations between cardiac size and race performance. Whilst Henschen *et al.*, (1899) thought that this was a beneficial adaptation, the prevailing view in the early 20th century was that cardiac hypertrophy secondary to athletic training was a pathological process due to the overload associated with exercise (Bryan *et al.*, 1992). Opinion has now changed however, and there is general consensus that the athletic heart syndrome represents a variety of adaptations that allow normal or improved function in contrast to the dysfunction seen in cardiac pathologies. The changes documented in athletic heart syndrome include overall increase in left ventricular mass, morphological changes of the left ventricle including increases in the diameter of the chamber and increases in the thickness of the walls that make up the chamber.

However, the fact that many cardiac pathologies result in increases in cardiac size and dimensions similar to those changes seen in athletic heart syndrome has led to the need for diagnostic criteria to rule out pathological processes in such cases. The

advent of echocardiography has meant morphological and functional tests may be performed with relative speed and ease, with little discomfort to the subject.

The left ventricle of the human heart has two functional layers of muscle, the sub - epicardial and the sub - endocardial layers. The second layer, a much smaller layer than the sub - epicardial layer, lines the inside of the ventricular cavity and the fibres of this layer connect the apex of the cavity to the mitral valve at its base. During contraction the cardiac fibres shorten in order to increase intra ventricular pressure and therefore eject blood. The fibres of the sub - epicardial layer contract and cause a reduction in the diameter of the chamber (known as the short axis of the chamber). The fibres of the sub - endocardium on the other hand cause a reduction in the length of the chamber (known as the long axis). Since the fibres of the sub - endocardium are connected to the mitral valve, when they contract, they pull the mitral valve down along the long axis of the ventricle. The motion of the valve may form the basis of a functional test of the ventricle in the differentiation of pathological and athletic heart syndromes. The basis of this thesis is to determine whether there are differences in the movement of the mitral valve between athletic groups and groups with pathological increases in heart size, and to determine whether these differences allow for assessment of the nature of increased cardiac mass.

CHAPTER 2: LITERATURE REVIEW

2.1 INTRODUCTION

The layers of the cardiac walls are well documented in many physiology texts. These layers comprise the fibrous and serous pericardium, the epicardial muscle layer and finally on the innermost surface, the endocardial layer. What is less commonly described is that, in terms of cardiac function there are two layers of cardiac muscle, the sub - epicardial layer, and the sub - endocardial layer (Heinen & Gibson 1999). The importance of this comes from the fact that the muscle fibres that make up these layers do not run in the same direction. The fibres of the sub - epicardial layer are circumferential and can be thought of as forming loops around the ventricle. The second layer, the sub - endocardial layer are longitudinally orientated and connect the apex of the heart to the mitral or aortic valves. These longitudinal fibres have specific properties that make their response to changes in cardiovascular function or disease unique. This review will focus on the properties of these fibres, and recent developments in their study.

2.2 FIBRE ORIENTATION OF THE LEFT VENTRICLE

Central to the work on sub - endocardial function is the notion that the fibres of the myocardium that make up that layer are longitudinally oriented. However, it would be an over simplification to state that sub - endocardial fibres run in a straight line from the apex of the ventricular cavity to the base. Pearlman *et al.,* (1982), performed careful dissection of both hypertrophied and normal ventricular walls of human hearts.

Following dissection, the fibres of each layer of the cardiac tissue were characterised by their α angle. The α angle is the angle between the orientation of the fibre and the circumferential direction. If the result is plotted against the depth of wall from which the fibre came, the graph shows a smooth curve from -45° on the sub epicardial layer to $+45^{\circ}$ at the level of the sub endocardium (see Figure 2.1). In addition, while fibre angle may change relatively smoothly through the transmural depths, by far the majority of fibres are in the + 30 to - 30° portion of the heart, with relatively few fibres (less than 5 %) lying in the $+45^{\circ}$ range. It is evident therefore that with increasing depth through the myocardium a greater component of fibre contraction force can be resolved into the longitudinal direction. Ultimately at the level of the sub - endocardium, at least half of the contraction force generated by the myocyte will act along the long axis and draw the base and apex of the chamber together. Furthermore, the fibres of the trabeculae on the interior surface of the ventricle are entirely longitudinal (Greenbaum 1981). In terms of functional capacity only the innermost 7 - 10 % of fibres contribute significantly to the movements within the ventricle along the long axis (Pearlman 1982; Jones 1990). It is evident therefore that the fibres that make up the sub - endocardial layer, connect the base to the apex via a spiral configuration of fibres. During systole, the activation of the sub - endocardial fibres cause the base and apex to be drawn together inside the chamber in a wringing action (Jones 1990).

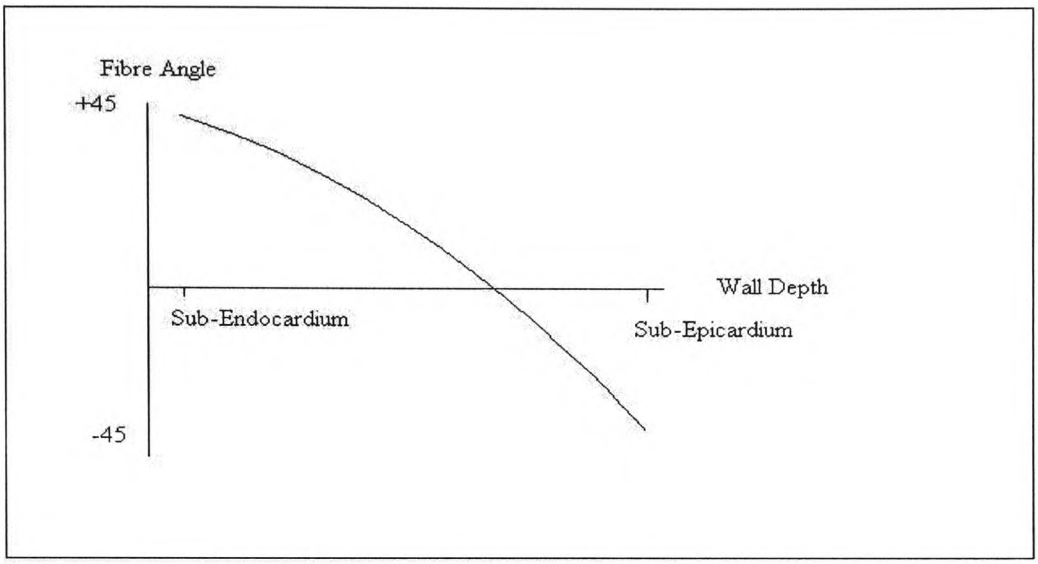

Figure 2.1 Schematic showing the change in fibre angle (α angle) relative to the circumferential axis in human hearts. Note the smooth transition from $+45^{o}$ in the sub - endocardium to -45^{o} in the sub - epicardium.

The whole heart does not rotate however, as the fibres of the sub - epicardium serve to pull the base and apex together with a wringing motion in the opposite direction, as the α angle of these fibres is roughly equal but opposite to the sub - endocardial fibres. Furthermore, the posterior of the heart is fused to the mediastinum of the thoracic cavity (Tortora & Grabowski 1997), and the apex of the heart is held by the most connective tissue and is functionally stationary through out the cardiac cycle (Palka *et al.,* 1995; Heinen & Gibson 1999). The result of this is that longitudinal ventricular dynamics cause the base of the ventricle to move towards the apex during systole and away from the apex during diastole.

While it is evident that these fibres are not solely longitudinal in their direction of action, in terms of echocardiographic evaluation the rotational component of their contraction cannot be measured at the same time as longitudinal movements, as it would occur at approximately 90^{o} to the incident ultrasound beam (Feigenbaum 1994). Therefore since only apical or basal movements of these fibres will show up on the echocardiogram only the longitudinal component of their movement can be measured, and thus the term longitudinal function has been used to describe their movements.

2.3 Longitudinal Function: The Role of the Mitral Annulus

The leaflets of the mitral valve insert into the sub - endocardium. At the point of insertion there is a thickening of the trabeculae (Jones 1990), this thickening forms a continuous ring around the inside of the ventricle, which is termed the mitral annulus.

As discussed previously, the longitudinal directed contractions inside the left ventricle make the base of the heart oscillate through the cardiac cycle. This means that the mitral annulus is pulled towards the apex of the heart during systolic contraction and moves away from the apex during diastolic relaxation. Measurements of the velocity and displacement of the mitral annulus form the basis of long axis investigations. As the movement of the mitral annulus has been used to estimate longitudinal contractions, the literature contains several terms; mitral annular movement, long axis function, longitudinal function or sub - endocardial function to describe the same measurements. The introduction of tissue Doppler echocardiography (TDE) means that the peak velocities of the mitral annulus as it moves in systole and diastole can be measured with relative accuracy and speed.

There is no reason why, using echocardiography, contraction and relaxation velocities along the long axis cannot be measured at points other than the mitral annulus, however, measurements of this site have emerged as the most popular due to its high reproducibility (Fraser *et al.,* 1999). This is because the longitudinal contraction velocity of the sub - endocardium increases as the distance from the apex of the ventricle increases (Pai *et al.,* 1998). Since the mitral annulus is the most basal portion of the ventricle, it undergoes the largest longitudinal velocity changes through the cardiac cycle. Therefore as the annulus achieves the greatest longitudinal velocities it causes the greater Doppler shift and this may be responsible for the greater reproducibility of annular measurements over other measurements along the ventricular long axis (Fraser *et al.,* 1999).

The mitral annuls is also a useful landmark that can reduce inter - observer variability. Small discrepancies in the position of the sample volume within the sub - endocardial wall tissue could contribute to large differences in measured contraction velocities. The use of the annulus as an intra - myocardial landmark reduces the variability that may be introduced by taking samples at less obvious sites within the sub - endocardium. As already stated contraction velocities increase with distance from the apex (Pai *et al.*, 1998) therefore contraction velocities can vary greatly within the sub - endocardium even within the same ventricular contraction. Consequently the ability to repeatedly sample tissue velocities from as close to the same site is paramount.

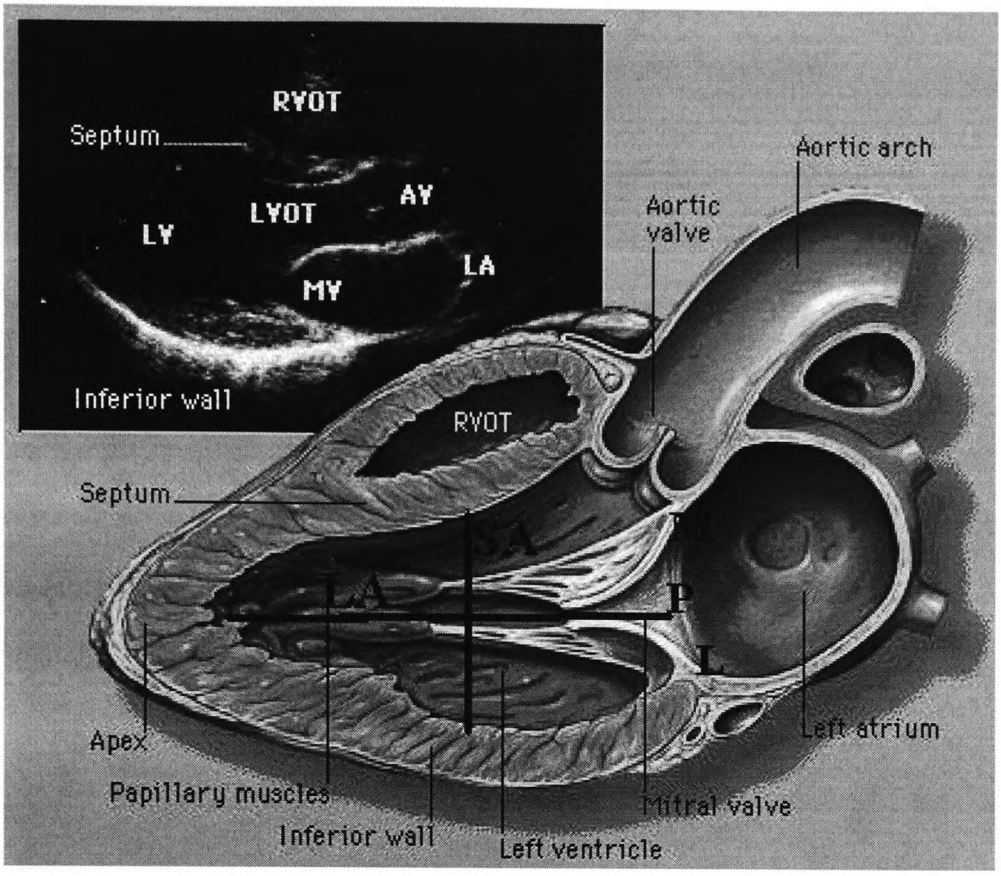

Figure 2.2 The left vetricle during supine echocardiographic evaluation with the short axis (SA) and long axis (LA) identified. Three of the common measurement sites are identified lateral (L), medial (M) and posterior (P), anterior annular site not shown. During the cardiac cycle these points of the annulus oscillate. the apex remains stationary thus the annular points move towards the apex in systole and away during diastole.

2.3.1 MITRAL ANNULAR MOTION THROUGHOUT SYSTOLE

During systole, the fibres of the sub - endocardium are activated prior to the fibres of the epicardium. This is due to myocyte depolarisation, which spreads from the endocardial to epicardial layers, (Julian & Cowan 1992). Since the sub - endocardial fibres are activated first, they play a significant role in the isovolumetric contraction phase (IVCP) of systole. During this phase, the geometry of the ventricle changes to become more spherical as the longitudinal force production pulls the mitral annulus towards the apex before any activation of circumferential fibres. Using tissue Doppler Echocardiography (TDE), which will be covered later in this review, this early activation velocity in the longitudinal direction can be identified, and is usually termed the 1st systolic wave (Sw1 also identical to IVCP). Shortly after this, the circumferential fibres are activated and short axis reduction begins, which is quickly followed by opening of the aortic valve. As intra - ventricular pressure and volume drop in the ejection phase, the longitudinal fibres are able to contract further, creating a second systolic wave (or Sw2) that can also be measured using TDE (Jones 1990). However, there has been some confusion of terms in the literature, with some investigators measuring peak systolic velocity and some measuring both Sw1 and Sw2.

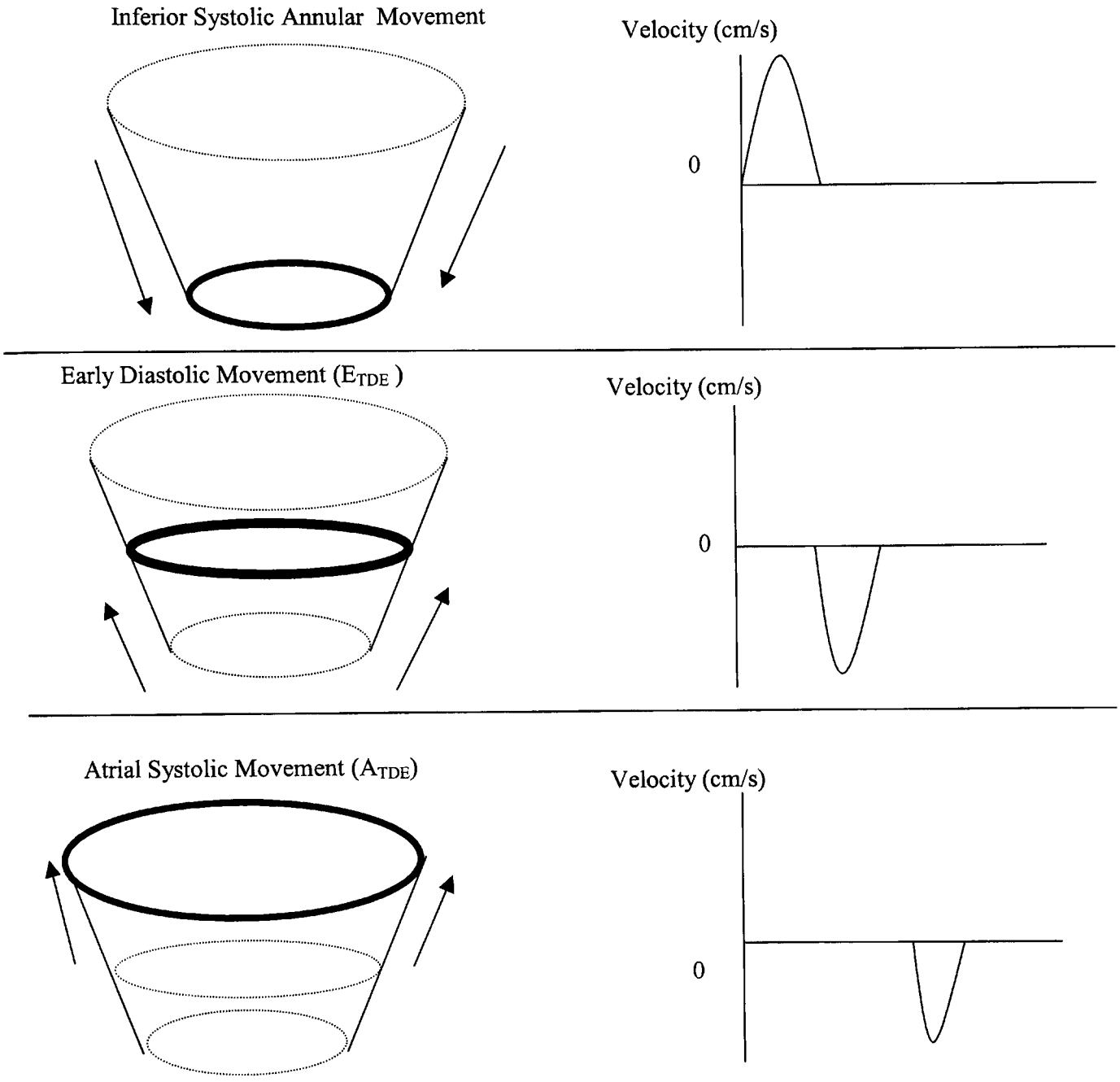

Figure 2.3 Representation of the movement of the mitral annulus throughout the cardiac cycle. The Pictures on the left represent annular displacement, with final annular position shown by the dark line. Systolic descent has been simplified to a single movement. The graphs on the right represent plots of the annular velocity against time for each phase of the cycle.

2.3.2 MITRAL ANNULAR MOVEMENTS DURING DIASTOLE

Following ventricular ejection and aortic valve closure there is little movement of the mitral annulus during the isovolumetric relaxation phase (IVRP). However, during early diastolic filling, there is rapid lengthening of the long axis of the ventricle as the mitral annulus ascends with the combination of myocyte relaxation and ventricular filling. The velocity of relaxation along the long axis in early diastole can be measured by TDE as it is demonstrated by a specific peak. This is termed the early relaxation wave (E_{TDE}). It is important to differentiate this from the measurement of blood flow across the mitral valve during early diastole, which is termed (E). E_{TDE} refers to tissue velocities measured using tissue Doppler, while E refers to blood velocities measured using traditional Doppler. After the early rapid filling of diastole, atrial systole takes place, this has a dual function, obviously, it serves to maximise ventricular end diastolic volume. However, in addition, the atrial contraction pulls on the mitral valve and raises the 'roof' of the ventricular cavity. This increases the potential volume of the ventricle, and creates a second lengthening of ventricular myocytes along the long axis. This also can be measured using echocardiography and is termed A_{TDE} (again different from haemodynamic flow across the mitral valve during atrial systole known as A).

2.4 Studies of Mitral Annular Motion Prior to Tissue Doppler Echocardiography

Before the advent of TDE, the use of mitral annular motion to investigate long axis function was limited. However, some researchers had realised that measurement of longitudinal shortening of the ventricle could be made, even in subjects whose echocardiograms had poor endocardial definition, a source of error in the assessment of ventricular volume and ejection fraction (see section 2.5). Keren *et al.*, (1988) examined the timing of mitral ring movement in relation to haemodynamic inflow in healthy and diseased patients. The results indicated that a mitral annular descent of approximately 12.8 mm, coincided with early pulmonary venous inflow into the left atrium, furthermore the descent of the annulus served to increase the volume of the atrium and assist atrial filling. The annular descent ended simultaneously with the end of aortic outflow. Early diastole followed 100 ms later and was typified by a rapid elastic recoil of the annulus (of ~ 10 mm), that aided ventricular filling by reducing ventricular pressure (termed ventricular suction), also some of the blood in the lower atrium was by default displaced into the ventricle as the mitral valve ascended around it. This was followed by a small annular movement of (2 mm) during atrial systole. This was confirmed by Simonson *et al.*, (1989) who examined the mitral annular systolic displacement in healthy and diseased subjects. Although their conclusion of a 12 mm systolic displacement of the annulus was largely in agreement with Keren *et al.*, (1988), their data went further for two reasons. Firstly, they demonstrated a direct correlation between mitral annular displacement during long axis shortening and

ejection fraction (r = 0.78 SEE = 12 %). Secondly, they determined that long axis systolic displacement was reduced in patients with hypertension, coronary artery disease (CAD), hypertrophic cardiomyopathy (HCM) or dilated cardiomyopathy (DCM). Furthermore, they were able to demonstrate, from the strong correlation, and reduced function in disease, that a total systolic displacement of 8 mm or less identified subjects with reduced ejection fraction (sensitivity 82 % and specificity 98 %). This was the first evidence to establish the importance of long axis function in the diagnosis of diseased hearts. It is interesting to note, that despite the good correlation achieved here, more recent evidence has demonstrated that both long axis displacement and velocity are more reliable in the diagnosis of disease than ejection fraction. This was first seen by Jones *et al.,* (1990) who examined long axis function in healthy and diseased subjects (mitral valve disease) by examining the increase in the sphericity of the ventricular cavity during the IVCP. Their results indicated that the diseased group displayed a reduction in the degree of sphericity during IVCP and sphericity was completely absent in those who had undergone mitral valve replacement. Once again, this indicated a reduction in function in diseased states. It also demonstrated the sensitivity of long axis measurements, as the orthodox measurements of systolic function (ejection fraction, fractional shortening) were all normal in the diseased group. Following this Toumanidis *et al.,* (1992) developed a novel method of assessing mitral annular movement. They hypothesised that since at the end of systole, the mitral annulus was 'low' and constricted, and at the end of diastole it was 'high' and wide open, then the annulus followed the approximate geometric shape of a truncated cone (see Figure 2.3). Their study investigated the

relation of the approximate volume of this cone to systolic function and found a significant correlation between the volume of the cone and ejection fraction.

2.5 TISSUE DOPPLER ECHOCARDIOGRAPHY

Conventional Doppler investigation of the heart was initially developed to investigate blood flow velocities and patterns, within the cardiac chambers. This was possible because of the relatively high speed with which blood moves through the chambers of the heart (~ 70 cm s^{-1}) generating a higher Doppler phase shift. It was performed with either continuous wave Doppler, which allowed the generation of colour coded blood pools, with the direction and velocity determining the colour at any particular point on the image. This enabled the analysis of overall blood flow, but could only determine average velocities over a specific period. The determination of a peak flow velocity was performed by pulse wave Doppler. This has the additional advantage of inherently higher temporal resolution than colour flow mapping allowing for rapid changes in blood flow to be quantified (Feigenbaum 1994). However, following appropriate changes to the hardware and software used to encode this Doppler information it was possible to derive information about the velocities of the much slower moving (6 - 24 cm s^{-1}) myocardium (Sutherland *et al.*, 1995). These changes filter out the lower amplitude blood echoes and let the tissue echoes through the appropriate filter. In addition, it is possible to acquire either continuous wave data for the analysis of overall wall motion or pulse wave data for the determination of a peak velocity within a specified sample area.

2.5.1 VALIDATION OF TISSUE DOPPLER ECHOCARDIOGRAPHY

Since tissue Doppler echocardiography is relatively new and much of the work in this review concerns information obtained using TDE, it is necessary to give a brief overview of the accuracy and validity of the technique.

2.5.1.1 VALIDATION IN VITRO

The majority of work performed to validate TDE in vitro used 'tissue mimicking' phantoms. These are synthetic disks with similar acoustic properties to human soft tissue. Hence measurements made on tissue phantoms are generally reproducible in human experiments (Sutherland *et al.,* 1994). Using a phantom disk rotating in water Sutherland *et al.,* (1994) performed a series of studies to determine the properties of velocity resolution and energy maps. The disk was rotated at known speeds within the velocity range expected from contracting myocardium. The results demonstrated that encoded velocities were within 5 % of the actual velocity, however the further the velocity range setting of the machine from the actual velocity the greater the error. Further tests were conducted using a similar phantom by Fleming *et al.,* (1994) to test the effect of different machine settings on the velocity resolution. It was shown that increasing the Doppler receive gain setting had a detrimental effect on velocity resolution. Lange *et al.,* (1997) investigated the ability of TDE to assess the volume of an artificially contracting phantom compared to traditional grey scale measures. TDE demonstrated better estimation of both maximal and minimal phantom volumes. Lange *et al.,* (1998) further confirmed this by demonstrating that while both grey scale

and TDE assessment of contracting phantom volume tended to underestimate the true value, the systemic error was less using TDE (- 1.2 %) than grey scale images (- 4.3 %). These results taken together indicated that with appropriate machine settings, the re - devised algorithms had the potential to determine with relative accuracy velocities and volumes within the myocardium.

2.5.1.2 VALIDATION IN VIVO

Lange et al., (1995) evaluated the validity of TDE in vivo by comparing TDE derived velocities with velocities from canine hearts with piezo electric crystals embedded in the epicardium, mid wall and endocardium. The results were similar to the in vitro work of Sutherland et al., (1994) as the agreement between TDE and piezo electric output was within 5 %. In addition, the reduction in transmural velocity gradient induced by acute ischaemia was detected and accurately measured by TDE.

Other animal studies have been used in the validation of TDE, Sutherland *et al.,* (1994) detected reductions in systolic wall velocities in pigs following acute coronary occlusion and a return to normal wall velocities following reperfusion. In addition, Garcia *et al.,* (1995) demonstrated that the reduction in ventricular wall velocities could be detected earlier using pulsed wave TDE due to its inherently superior temporal resolution. Fleming et al., (1996) validated TDE against velocity data obtained from digital post processing of traditional grey scale M - mode images. The results demonstrated TDE accurately displayed the velocity and direction of wall motion. Furthermore, it was faster, more reliably and easier to interpret than M - mode

images. Lange *et al.*,(1994) determined a high degree of accuracy between TDE assessment of morphology, volume and attachment site of an intra - ventricular cardiac mass, and post - operative and pathologic findings. Lange *et al.*, (1997) also determined good agreement between in vivo assessment of end systolic and end diastolic volumes, between TDE and traditional M - Mode measures, and further defined TDE validity by comparing measures of ventricular volumes with cineventriculography (Lange *et al.*,1998). The results of this study determined that TDE had a significantly closer agreement (with cineventriculography) than did traditional grey scale images.

The reason for improved estimation of cardiac volumes and velocities using TDE is due to two related factors. Grey scale M - Mode or two - dimensional images rely on the signal strength to determine the brightness of each generated screen pixel. Grey scale definition of the endocardial border is generally poor. Small structures such as the trabeculae prevent sharp boundary definition and reflect a small amount of the transmitted signal. Furthermore, this reflected signal must travel through intervening cardiac tissue, and thoracic structures all of which reduce signal strength. Therefore, M - mode estimations of volumes or velocities that require endocardial border definition are liable to have systemic errors in grey scale evaluation. Both types of Doppler echocardiography (traditional and tissue) however, are dependant upon measurement of the phase shift between outgoing and returning signals, and are independent of signal strength (Fleming *et al.*, 1996). Therefore, signal strength

reduction due to cardiac and thoracic tissue is of no consequence, and both visual endocardial definition and velocity resolution at the endocardial border are enhanced.

2.6 Tissue Doppler Echocardiographic Assessment of Mitral Annular Systolic Descent Velocities

Tissue Doppler echocardiographic assessment of mitral annular velocity has been suggested as a measure of both systolic and diastolic ventricular function that may be less affected by filling pressures. Oki *et al.,* (1999) investigated the role of systolic wall motion velocities using TDE in healthy subjects, both in the sub - endocardial and sub - epicardial layers. They determined that the longitudinal fibres of the sub - endocardium played a greater role in early systole and the sub - epicardial fibres had a greater role in the ejection phase of systole. In addition, TDE measures of mitral annular systolic descent velocity have been shown to be extremely sensitive to changes in contractility. Gorscan *et al.,* (1998), compared TDE measured annular velocities with standard echocardiographic indices in response to incremental low dose dobutamine infusion (a cardiac ionotrope) to determine myocardial viability post infarct. The infusions were at stated doses of 1, 2, 3 and 5 $\mu g\ Kg^{-1}\ min^{-1}$. Routine measures of percent wall thickening at systole or ejection fraction did not change at all until the 5 $\mu g\ Kg^{-1}\ min^{-1}$ dose was reached. The annular descent velocity was significantly increased at the $1\mu g\ Kg^{-1}\ min^{-1}$ in level and further increases occurred at every subsequent dose level. Whilst this has obvious implications for patient safety in pharmaceutical stress testing it also neatly demonstrates how TDE analysis of mitral

motion can detect subtle alterations in contractility that would be missed by standard echocardiographic procedures.

Clinically hypertrophic cardiomyopathy (HCM) is diagnosed by the presence of increased left ventricular mass (LVM) in tandem with myocyte disarray. However, a significant proportion of individuals do not display increases in LVM but are genotype positive for the disease. In such subjects, there is significant myocyte disarray and dysfunction that would lead to reduced contraction velocities despite apparently normal measures of global cardiac function (ejection fraction, fractional shortening, mitral E / A ratio). It is therefore a reasonable assumption that 'non LVH HCM' may be identifiable using TDE measures of mitral annular velocities. Nagueh *et al.*, (2000), examined the capability of TDE annular assessment to successfully identify HCM irrespective of presence or absence of increased LVM in a transgenic rabbit model of human HCM and compare the results to wild type and non transgenic rabbits. In their cohort, nine of 24 (37.5 %) rabbits with HCM genotype failed to display any increases in LVM. Transgenic animals displayed significantly lower systolic velocities, independently of an increased LVM, than the non transgenic or wild type animals. A systolic velocity of < 8.5 cm s^{-1} had a sensitivity of 86 % and specificity of 100 %. This has important implications for the future of echocardiographic screening for diseases such as HCM, and whilst animal studies do allow more control over genotype in group selection, more studies on humans are needed.

Tabata *et al.*, (2000) examined systolic descent of the mitral annulus using TDE in patients with asymmetric HCM (interventricular septum: posterior wall ratio > 1.3) compared to controls. Their data demonstrates reduced sub - endocardial contraction velocities in the septal area of the sub - endocardium in the HCM group. It is interesting to note however, that there were also significantly reduced contraction velocities in the sub - endocardium of the non - hypertrophied wall (posterior wall in this case). As none of the HCM group displayed any excessive intra - ventricular pressures, it is likely that in these subjects the apparently normal posterior wall has been significantly affected by the pathological HCM process. Mishiro *et al.*, (1999) also looked at long axis function in patients with HCM. They determined that the HCM group had significantly lower long axis systolic (Sw1 and Sw2) velocities than the control group. In addition, the time from the Q wave on the ECG to the peak systolic velocity during either Sw1 or Sw2 was longer in the HCM group indicating a reduced rate of force production.

Early work using TDE assessment in humans also focused on determining whether peak long axis descent velocities during systole could be used as a measure of global systolic function. As previously mentioned Gorscan *et al.*, (1999) demonstrated that mitral annular movement was more sensitive to pharmacologically induced changes in systolic performance than was ejection fraction. It is therefore likely that mitral annular descent velocity will be a reasonable index of global systolic performance. Prior to the availability of commercial TDE machines, mitral annular descent displacement or average descent velocity (displacement / time) had already been

suggested as a useful tool in the evaluation of systolic function (Pai *et al.,* 1991; Simonson *et al.,* 1989; Jones *et al.,* 1990). However, this technique did require off line analysis of mitral annular motion, which was time consuming and correspondingly did not enjoy frequent use in the clinical setting. After the introduction of TDE, Gulati *et al.,* (1996) investigated the correlation between an average of the systolic descent velocities of six sites of the mitral annulus and compared them with ejection fractions measured using radionuclide ventriculography. The subjects all had a range of cardiovascular diseases (coronary artery disease (CAD), dilated cardiomyopathy (DCM), hypertension, pulmonary hypertension). The results demonstrated a strong linear relationship between the average of the six - site descent velocity and ejection fraction. ($r = 0.86$, $p < 0.01$, SEE 1.02 cm s^{-1}) with a regression line expressed by the equation:

Ejection Fraction = 8.2 (Average Annular Velocity) + 3 %.

In addition, this relationship seems to hold true over a wide variety of ejection fractions, (range 18 - 82 %). In order to determine a functional test, the investigators found that a mitral annular descent velocity of greater than or less than 5.5 cm s^{-1} had sensitivity, specificity and accuracy of 88, 97 and 93 % respectively for identifying individuals with ejection fractions of above or below 50 %. (see Table 2.1)

Table 2.1 Sensitivity and specificity plots for determining left ventricular ejection fraction from peak average mitral annular descent velocities, using a cut - off criterion of 5.5 cm s^{-1}

	Ave. E_{TDE} Vel. > 5.4 cm s^{-1}	*Ave. E_{TDE} Vel < 5.4 cm s^{-1}*
EF > 50 %	21 (**87.5 % Specificity** / True Negative)	3 (12.5 % False Negative)
EF < 50 %	1 (3.3 % False Positive)	29 (**96.6 % Sensitivity** / True Positive)

E_{TDE} = Annular velocity during early diastole, EF = Ejection fraction. (For this data a positive test indicates an ejection fraction of less than 50 %).

This is an important addition to the investigation of Gulati *et al.*, (1996) as it suggests that not only can TDE annular velocity be used in the assessment of global systolic function, the authors also suggest it is a sufficiently sensitive test for it to be used in clinical practice to replace the more time consuming off line analysis. Alam *et al.*, (2000) examined systolic descent velocities in subjects who had recently experienced their first myocardial infarct (MI). Like Gulati *et al.*, (1996) they found good correlation between systolic descent velocity and ejection fraction. They demonstrated that an average mitral annular descent velocity of 7.5 cm s^{-1} or greater predicted ejection fraction of 50 % or above (sensitivity 79 % specificity 88 %). This is a less powerful predictor than the 5.4 cm s^{-1} suggested by Gulati and co workers (1996). However, the difference may be due to a different population group, or the less

accurate estimation of ejection fraction by grey scale echocardiography by Alam *et al.*, (2000). The sensitivity of any test of disease is related to its prevalence in the population, and both Gulati *et al.*, (1996) and Alam *et al.*, (2000), used diseased subjects over 40 years of age. There must be some doubt over the use of their 5.4 cm s^{-1} or 7.4 cm s^{-1} to determine ejection fractions of above or below 50 % in younger apparently healthy populations. This is further substantiated as other investigators have reported a small but significant age dependant decrease in annular systolic descent velocity (Ohte *et al.*, 1999). Previously Alam *et al.*, (1999) attempted to address this problem and examined systolic descent velocity in apparently healthy controls. The correlation between ejection fraction and mitral annular systolic descent velocity was $r = 0.7$ ($p < 0.05$), but this study failed to define a specific velocity that would be indicative of reduced ejection fraction, this is may be due to few if any subjects having a reduced global systolic performance. Similarly Yamada *et al.*, (1999) examined the correlation between ejection fraction and peak systolic sub - endocardial contraction velocity in a variety of patients including DCM, ischaemic heart disease, hypertensive heart disease, asymmetric HCM with non - cardiac chest pain subjects to serve as controls. The results demonstrated a significant correlation between ejection fraction and peak average systolic annular descent velocity ($r = 0.59$, $p < 0.05$) and a strong inverse relation between ejection fraction and the duration from the Q wave on the ECG to the peak systolic velocity ($r = - 0.79$, $p < 0.05$). Due to the diverse pathologies and control group utilised in this study it provides powerful evidence that long axis dynamics can be used to rapidly evaluate global systolic function. However, it is disappointing that the authors failed to report a specific cut off

value that could be used to distinguish poor and preserved global pump function. The strong correlation between variables does not constitute a diagnostic test. Such a test requires the identification of specific values that are normal or abnormal.

The fact that reduced long axis systolic function has been so well correlated with ejection fraction in a number of studies has led to the intriguing possibility of using resting mitral annular systolic velocities to predict exercise capacity. Vinereanu *et al.*, (2001) investigated this in a group of asymptomatic (NYHA class IIa or lower) patients with severe aortic regurgitation. Following maximal exercise testing, the group was split in two, those who maintained ejection fraction and those whose ejection fraction fell during exercise. At rest, there were no differences in traditional measures of systolic function (ejection fraction or fractional shortening, end systolic wall stress) between the two groups. The systolic annular descent velocity however, did differentiate between groups and was significantly lower at rest in the group whose ejection fraction fell during exercise. Following correlation with the exercise capacity, a resting peak systolic descent velocity below 9.5 cm s^{-1} predicted poor exercise tolerance (specificity 90 % sensitivity 100 %).

While the possibility of resting prediction of exercise capacity from mitral annular descent velocities is intriguing and certainly from the data of Vineranu *et al.*, (2001) warrants further investigation, the subject group here are of an asymptomatic volume overload type, so there is a possibility that there is significant Frank - Starling activation even at rest since they are asymptomatic. If this is the case then the reduced

resting annular velocity in the group with a fall in ejection fraction during exercise may be a symptom of the break down of the Frank Starling mechanism and reduced long axis compliance at rest. If this is true, the predictive value of 9.5 cm s^{-1} suggested by the authors would remain valid for patients with volume overload pathologies. However, it may not be applicable to the general population, in which at rest Frank - Starling activation may be far less, and hence normal subjects with resting systolic annular velocities below 9.5 cm s^{-1} may have normal exercise capacity.

Other investigators focused on sites of ischaemia or infarcts and their relationship to regional annular motion abnormalities, and whether TDE was sufficiently sensitive to perform the opposite operation and identify a site of possible ischaemia or infarct by identifying regions of abnormal myocyte function, that could not be determined from global cardiac function. Fukuda *et al.,* (1998) examined mitral annular systolic descent velocities in patients with either ischaemic cardiomyopathy and dilated cardiomyopathy all of whom had suffered prior infarcts. The systolic descent velocities at the site of infarct were significantly lower than that at other sites on the same subject. Additionally, both cardiomyopathy groups also demonstrated lower systolic descent velocities at each of the six sites around the mitral annulus compared to controls. There were also significant correlations between the average of the six site descent velocities and ejection fraction (as previously documented by Gulati *et al.,* 2000). This suggests that TDE analysis of systolic annular motion allows for both regional assessment (by identification of specific sites of infarcts) and global assessment of systolic function (by the close correlation of the six - site average

prediction and ejection fraction). Similarly, Alam (2000) examined the heterogeneity of descent velocity between four sites of the mitral annulus in patients who had recently had an MI. His results demonstrated a reduction in mean mitral annular descent velocity in the MI group and a specific reduction in the mitral annular descent velocity at the site that corresponded to the area of infarct

Dagianti *et al.,* (2000) demonstrated that the region of an infarct reduced the systolic descent velocity in the corresponding area of the mitral annulus, indicating the infarct area was spread across the sub - endocardial portion of the ventricular wall. In addition, following exercise stress testing, there were transient reductions in annular descent velocity. The specific area of the reduction of annular descent velocity was related to specific stenosis within the coronary arteries as defined by coronary arteriography. Thus, patients with left anterior descending (LAD) artery stenosis had post exercise asynergies in anterioseptal and / or posterioseptal regions of the annulus. Subjects with left circumflex artery stenosis had reduced lateral and / or inferior annular movement, whilst right coronary artery blockage was associated with reduced inferior and / or posterioseptal annular systolic descent velocities. These findings suggest that TDE annular assessment can not only identify an area of infarct, but used with exercise stress testing, it may be possible to develop a relatively sensitive test to detect areas of reduced coronary blood flow, secondary to major artery stenosis. Such a test would have practical and financial advantages over coronary angiography, especially in reference to mass testing. This work was followed more recently by Cain *et al.,* (2001). Their investigation examined the possibility of using TDE assessment

of sub - endocardial function to assess reductions in function along the long axis during dobutamine infusion, in patients with known but sub - clinical coronary artery disease (i.e. an angiographicaly determined stenosed artery but no pain or reduction in exercise capacity, NYHA class II or lower). The results determined that there were significant reductions in both the peak systolic descent velocity and the time to peak velocity of the sub - endocardium in regions subtended by a stenosed artery, compared to segments with apparently normal perfusion. In addition, the extent of the reduced sub - endocardial function varied significantly between patients according to the amount of jeopardised myocardium resulting from the specific stenosis. This suggests that an increase in the heterogeneity between annular segments during dobutamine stress echocardiography may be one method for determining areas of reduced blood flow or ischaemia secondary to coronary artery stenosis. Also the area demonstrating reduced function may give an indication as to the amount of cardiac tissue at risk from a future infarct.

TDE measurement of annular movement has enabled assessments of the global and regional cardiac function in a wide variety of pathologies to be more sensitive. Fonseca *et al.,* (2000) demonstrated that in familial amyloidotic polyneuropathy (FAP), a lethal disease that leads to increased LVH in the latter stages, there are significant reductions in systolic function, specifically in annular descent velocities even before any changes in wall thickness or systolic function occur. This indicates that the changes in cardiac mass seen in the latter stages of the disease may be secondary to reductions in diastolic function rather than a direct effect of the disease.

Other potential uses for mitral annular TDE assessment includes use of reduced systolic descent velocities as a marker of rejection in patients receiving heart transplants (Mankad *et al.*, 1999).

2.7 TDE Mitral Annular Assessment of Diastolic Function

A variety of measures have traditionally been used to evaluate left ventricular diastolic function, these include, E and A mitral inflow velocities integral, and their ratio (with a preferred ratio of E / A of between 1 - 2), E wave deceleration time and isovolumetric relaxation time. TDE assessment of wall relaxation velocities also exhibits the characteristic early diastolic and atrial systolic peaks, (E_{TDE} and A_{TDE}). Lange *et al.*, (1997) attempted to determine if there was a similar pathological pattern to the E_{TDE} / A_{TDE} ratio. They examined two types of HCM. One with relaxation abnormalities and one with a restrictive inflow pattern, and compared them to controls. They demonstrated that in both pathological states the E_{TDE} / A_{TDE} ratio was always less than 1 (annular ascent velocities during atrial systole were always greater than in early filling), and this was true independently of the level of diastolic dysfunction. This is an indication of an increased force of atrial contraction in order to normalise the end diastolic ventricular volume, as early diastolic filling is inadequate. However, the control group always had E_{TDE} / A_{TDE} greater than 1. This paper laid the foundations for the current recommendations for E_{TDE} / A_{TDE} of less than 1 to be treated as suspicious and above 1 to be treated as normal.

Further to this one of the potential uses for TDE analysis of annular movement is to differentiate pathological hearts with pseudo - normal E / A ratios and those with truly normal E / A ratios. Caires *et al.,* (1998) examined both the E / A ratio and E_{TDE} / A_{TDE} ratio in patients with chronic renal failure exhibiting left ventricular diastolic dysfunction. Using the haemodynamic E / A ratio (the velocity of blood flowing across the mitral leaflets) 44 % (n = 21) of the cohort exhibited apparently normal ratio (E / A between 1 - 2). However, when the cohort was stratified using E_{TDE} / A_{TDE} only 27 % of the group displayed a normal pattern. This suggests that 17 % of the group displayed pseudo - normalisation of the haemodynamic mitral E / A ratio, and that TDE analysis was a more sensitive tool for establishing diastolic dysfunction.

Farias *et al.,* (1999) examined the ability of TDE mitral annular assessment of early diastolic velocity to distinguish between normal transmitral filling profile and restrictive, pseudonormal and relaxation failure profiles. Early relaxation velocity (E_{TDE}) was identified by Spearman rank correlation as the best single discriminator between control subjects and those with diastolic dysfunction. Similarly Bruch *et al.,* (1999) also examined the use of TDE assessment of mitral annular relaxation velocities to evaluate LV diastolic function in normal and diseased subjects (CAD and Hypertension). The traditional echocardiographic Doppler data was not significantly different between groups. The E_{TDE} velocities were different between groups, with the hypertensive group displaying the lowest relaxation velocities. Like Farias *et al.,* (1999) the data indicated that there was a reduced relaxation rate even in the presence of increased end diastolic pressure, as is seen in pseudonormalisation of diastolic

function. The investigators demonstrated that an annular E_{TDE} peak relaxation velocity of < 7 cm s^{-1} and an E_{TDE} / A_{TDE} ratio of < 1 had a sensitivity of 77 % and specificity of 88 % in identifying subjects with pseudonormalisation of mitral E / A inflow patterns (which were confirmed by intra ventricular catheterisation). Additionally, there was no correlation between end diastolic pressure in the left ventricle and peak early relaxation velocities, strongly suggestive of the fact that annular diastolic kinetics are preload independent, unlike traditional echocardiographic measures such as E / A ratio.

In patients with pathologies of volume overload TDE analysis has been shown to give successful quantification of the diastolic function of the left ventricle. Abe *et al.*, (1999) used TDE analysis of the mitral annulus to determine differences in regional diastolic function in patients with either mitral (MR) or aortic (AR) regurgitation. Their results demonstrated that MR and AR resulted in different filling patterns of the ventricle. AR was associated with depressed annular E_{TDE}, an increased time from aortic closure (determined by phonogram) to peak E_{TDE} velocity, and reduction in the long axis excursion during early diastolic filling. MR however, resulted in higher early relaxation velocities than AR and a reduced time from aortic closure to early relaxation.

Oki *et al.*, (1998) examined diastolic function of the left ventricle in hypertensives compared to controls. The results demonstrated impaired diastolic function as measured by TDE analysis of the long axis. The annulus had reduced peak early

relaxation velocity compared to controls and a concomitant higher atrial systolic velocity. Thus hypertensives demonstrated reduced E_{TDE} / A_{TDE} ratio. The hypertensives also demonstrated an increase in the time interval from the aortic component of the second heart sound (IIA) to the peak early relaxation velocity, indicating an impaired onset of myocyte relaxation. This was confirmed by a strong positive correlation between the IIA - Early relaxation peak duration and the time constant of early ventricular diastolic pressure decay during isovolumetric relaxation (for long axis $r = 0.74$, $p < 0.05$).

Ohte *et al.*, (1998), examined 56 patients with coronary artery disease. They compared mitral annular E_{TDE} velocities with LV end systolic index and the first derivative of left ventricular pressure decay (- dP / dt) and the time constant of left ventricular relaxation (tau) as measured with an intra - ventricular catheter. Peak annular velocity during early diastole was significantly correlated to pressure decay and negatively to tau and end systolic volume index. A multivariate regression analysis selected tau and end systolic volume index as the prime determinant of annular E_{TDE} velocity. This suggests that the annular velocity during early diastole is determined by both the lusitropic properties of the ventricular contractile apparatus since tau was one of the prime determinants and by the force of the preceding ventricular contraction since the negative correlation between end systolic volume index and annular velocity was the other prime determinant. This is important as it demonstrates that early diastolic performance may be influenced by both early diastolic relaxation and events at the end of systolic contraction. In subjects with stronger systolic contractions, there is a

concomitant increase in diastolic relaxation velocity, as though the systolic performance were responsible for some relaxation 'loading' effect. However, this is an inter - individual finding at rest, whether this would be the case within a single subject during contractions of increased force due to exercise for example is not yet known.

Transmitral inflow waveforms in elderly individuals can mimic those patterns observed in heart disease. Muller *et al.,* (1997) examined the effect of age on haemodynamic inflow patterns (E / A) and on TDE inflow patterns (E_{TDE} / A_{TDE}) in normal healthy subjects. Their results demonstrated that sub - endocardial E_{TDE} velocity (sub - endocardial fibres being responsible for long axis dynamics), were significantly age dependant, and that the decreased haemodynamic E seen in older subjects was due to a reduction in chamber compliance. Furthermore, the E_{TDE} / A_{TDE} analysis demonstrated that although absolute velocities were lower than those of younger subjects they were still within the normal range. Hence, older subjects may display an apparently pathological E / A ratio, but the assessment of the sub - endocardial E_{TDE}, identifies a normally functioning heart. This is supported by the work of Lindstrom *et al.,* (1999), who examined the effect of both age and pathology on mitral annular diastolic and systolic velocities. Their conclusions were that there was an age related decline in E_{TDE} function with older healthy subjects having lower E_{TDE} ascent velocities than younger healthy subjects. However, both groups had higher E_{TDE} velocities than did patients with either systemic hypertension or aortic stenosis. There was also a significant age related decline in systolic descent velocity of

the annulus, but again this was still significantly higher in older subjects than that in the diseased groups. This suggests that whilst there is a pronounced age related decline in both systolic and diastolic sub - endocardial function, these remain above the functional capacity found in certain diseased hearts. However, the data of Lindstrom (1999) does suggest that it is imperative that in cross sectional type investigations utilising different groups investigators must age match those groups. (See section 3.11)

Further to this Ohte and co workers (1999) examined whether early diastolic relaxation velocities would differentiate significantly between individuals with E / A ratio of less than 1 with CAD and older healthy subjects without CAD but demonstrating abnormal E / A ratio. The results were compared with the gold standard of LV end systolic index and tau (time constant for left ventricular pressure decay) measured by intra ventricular catheterisation. The annular relaxation velocities were as accurate as the measurement of tau and LV end systolic index in identifying whether subjects were CAD patients from healthy older patients. It is interesting therefore, that TDE assessment of diastolic relaxation velocities can identify pathology in hearts with pseudo - normal E / A ratio (Caires *et al.,* 1998; Farias *et al.,* 1999). Conversely, it may identify *'pseudo - pathology'* in older hearts that are actually healthy (Ohte 1999; Muller *et al.,* 1997)

Sohn *et al.,* (1997) evaluated the use of TDE annular diastolic ascent velocities in the assessment of global diastolic function. In their data, the healthy subjects displayed

E_{TDE} / A_{TDE} ratio's that were similar in value (between 1 - 2) to E / A ratios. The reduction in diastolic function associated with ageing, which is usually measured as a reversal of the E / A ratio (i.e. E / A < 1) was found only in subjects aged 60 and above. However, a reversal of the E_{TDE} / A_{TDE} ratio was demonstrated in subjects from 40 years and older. This suggests TDE assessment of ventricular relaxation along the long axis is potentially more sensitive to reduced diastolic capacity than global estimates of diastolic function such as haemodynamic mitral inflow information (E / A ratio). The proposed reason for long axis dynamics being able to identify this reduction in function in a younger age stratification was that while E_{TDE} relaxation starts simultaneously with mitral inflow (E), peak E_{TDE} velocity precedes peak E velocity and ends well before E mitral inflow. This means that in the final stage of early diastolic filling, there is a period when there is no lengthening of the ventricle along the long axis but blood flow is still being driven across the mitral valve, (as E_{TDE} has finished but E is still ongoing). The increasing blood volume of the ventricle must be accommodated by the compliance across the short axis of the ventricle during this latter portion of early ventricular filling. This is of importance, because if long axis lengthening stops before short axis lengthening, then by definition there is greater compliance across the short axis of the chamber than across the long axis. While this may seem intuitively correct due to the far greater muscle mass of the concentric fibres responsible for short axis dynamics, it is the basis for an important functional difference. If, in any healthy heart there is less compliance across the long axis than across the short axis, then in a heart with relaxation problems it is likely that the long axis will demonstrate abnormalities before either the short axis movement or global

diastolic function as measured by E / A ratios. Hence, in the work of Sohn *et al.*, (1997) the reversal of the E_{TDE} / A_{TDE} ratio was identified in an earlier age stratification than mitral E / A ratio.

2.8 TDE Assessment of LV Filling Pressure

The measurement of pulmonary capillary wedge pressure (PCWP) provides an indirect measure of left atrial pressure and is particularly useful in the diagnosis of left ventricular failure and mitral valve disease. The measurement is made by advancing a balloon - tipped, multi - lumen catheter from a peripheral vein into the right atrium, the right ventricle, and then into a branch of the pulmonary artery. There is one opening (port) at the tip of the catheter (distal to the balloon) and a second port several centimetres proximal to the balloon. These ports are connected to pressure transducers. When properly positioned in a branch of the pulmonary artery, the distal port measures pulmonary artery pressure (~ 30 / 15 mm Hg) and the proximal port measures right atrial pressure (~ 0 - 2 mm Hg). The balloon is then inflated with air using a syringe (the balloon volume is about 1 ml) and this occludes the branch of the pulmonary artery. When this occurs, the pressure in the distal port rapidly falls, and after about 10 seconds, reaches a stable lower value that is very similar to left atrial pressure (normally about 8 - 10 mm Hg). The recorded pressure during balloon inflation is similar to left atrial pressure because the occluded vessel, along with its distal branches which eventually form the pulmonary veins, acts as a long catheter which measures the blood pressures within the pulmonary veins (this pressure is

virtually the same as mean left atrial pressure). A PCWP exceeding 15 mm Hg suggests mitral stenosis, mitral insufficiency, severe aortic stenosis, aortic regurgitation, ventricular failure, or other cardiac defects or pathologies. When the PCWP exceeds 20 mm Hg, the transmission of this pressure back into the pulmonary vasculature increases pulmonary capillary hydrostatic pressure, which can lead to pulmonary congestion and oedema. Pulmonary capillary wedge pressures are also useful in evaluating blood volume status when fluids are administered during hypotensive shock.

Given that during early diastole the filling pressure is determined by left atrial pressure, then it is possible that the degree of miss - match between the rate of trans mitral inflow (E) and the rate of ventricular lengthening (E_{TDE}) may be an indicator of left atrial filling pressure. Nagueh *et al.,* (1998) examined the possibility of using TDE and traditional measures of mitral inflow velocities to estimate diastolic filling pressure in subjects with sinus tachycardia (ST). In ST the mitral inflow data may not display the normal E and A inflow peaks as these merge at high heart rates. If the E and A waves are present, they may be E or A dominant. Their data demonstrated that whilst there were weak but significant relations between individual measurements (annular velocities, mitral inflow velocities, or venous flow), there was a strong significant correlation between the E / E_{TDE} ratio and pulmonary capillary wedge pressure ($r = 0.86$). With an equation of

$$\mathbf{PCWP = 1.55 + 1.47(E / E_{TDE})}$$

The investigators further tested this equation in a prospective cohort of 20 subjects again with ST. There was a strong correlation between the echocardiographically predicted and catheter measured PCWP ($r = 0.91$) with a mean difference of 0.4 ± 2.8 mm Hg. Of further importance is that this predicted relationship was independent of the pattern of mitral inflow seen in the ST patients. This has implications outside of ST, for example during exercise stress testing, the higher heart rates often result in the merging of the E and A wave of the diastolic period.

Sundereswaran, Nagueh *et al.,* (1998) also used the same technique to assessboth PCWP and right atrial pressure (RAP) in patients who had recently undergone cardiac transplant. They measured both mitral and tricuspid early haemodynamic inflow (E) and early diastolic velocity at the annulus of both valves. (E_{TDE}). Similar to their previous findings PCWP was weakly related to all mitral variables but strongly to E / E_{TDE} ratio ($r = 0.8$; $PCWP = 2.6 + 1.46 (E / E_{TDE})$). Similarly, right atrial pressure related weakly to all tricuspid data, but was strongly related to E / E_{TDE} for the tricuspid valve, ($r = 0.79$; right atrial pressure $= 1.76 (E / E_{TDE}) - 3.7$). Furthermore, in a prospective study using 18 repeat right sided catheterisations the Doppler equation detected changes in RAP well, compared to the catheter measures (mean difference $0 \pm$ 3.45 mm Hg). Thus their conclusion was that the E / E_{TDE} ratio could be used to accurately estimate filling pressures in both ventricles, at least in cardiac transplant patients.

Following on from this work Nagueh, *et al.*, (1999) examined the ability to estimate left ventricular filling pressures in subjects with HCM using TDE assessment of annular diastolic velocity and normal Doppler trans - mitral flow and compare these findings to those from an intra - ventricular catheter. The results demonstrated that although E / flow propagation velocity ratio predicted diastolic filling pressure quite well (r = 0.67), the best estimate of filling pressure came from the E / E_{TDE} (i.e. the ratio of early mitral inflow to early tissue relaxation velocity) with a correlation of r = 0.76. Taken together the work of Nagueh and co workers suggests that E / E_{TDE} ratio may accurately be used to assess PCWP and RAP in a variety of pathologies, and further work to confirm this hypothesis using subjects with a variety of cardiac complaints is anticipated in the near future. Furthermore, the ability of E / E_{TDE} to predict these pressures even in the absence of specific E and A waves may have further applications in measuring haemodynamic responses to exercise.

2.9 Effect of Loading

One of the major reasons for the recent increase in interest surrounding annular dynamics is the suggestion that the data derived from its movements are less dependant upon preload than other measures of cardiac function. As described in previous sections the ability of TDE assessment of annular relaxation velocities to discriminate between normal and pseudonormal diastolic filling is powerful evidence of the preload independence of mitral annular movements. This has been further investigated by Alam *et al.*, (2000) who demonstrated that in subjects who had

suffered previous myocardial infarcts there was no correlation between E_{TDE} and mitral inflow variables suggesting that early diastolic relaxation velocities are not dependant upon preload. Aranda *et al.*, (1998) examined the effect of nitroglycerine infusion on heart transplant patients. The nitroglycerine infusion significantly reduced both preload (measured PCWP) and after load (MAP). However, despite these changes in loading there was no change in diastolic relaxation velocities, furthermore there were no significant correlations between diastolic relaxation velocities and PCWP, MAP or wall stress. The authors concluded that these factors therefore had no effect on resting myocardial relaxation velocities. However, the fact that all the subjects tested had been subject to heart transplants cast some doubt over the validity of this conclusion in relation to subjects without cardiac transplants. This was addressed by Sohn *et al.*, (1997) who examined the effect of either saline infusion or nitro glycerine on annular relaxation velocities. Group 1 who had been diagnosed with relaxation abnormalities and had E / A ratios of less than 1, received a rapid saline infusion of up to 2500 ml in order to increase preload to maximal levels. Group 2 were patients with cardiac disease but apparently normal systolic and diastolic function received a nitro glycerine infusion that increased every 2 minutes until an increase in heart rate of 10 bpm above resting levels was achieved. Group 1 demonstrated a shift in their E / A ratio towards a pseudo - normal profile due to increased filling pressure however, the E_{TDE} / A_{TDE} ratio was unchanged, as was the absolute E_{TDE} and A_{TDE} values. Group 2 displayed a decrease in the E / A ratio indicative of restrictive early diastolic filling. The E_{TDE} value and the E_{TDE} / A_{TDE} ratio however, were once again unchanged. These data indicate that long axis relaxation velocities are relatively independent of changes in

blood volume and preload, and unrelated to small changes in heart rate. It would be unwise to conclude from this data that E_{TDE} / A_{TDE} ratio was completely unrelated to heart rate, as a 10 bpm rise used in this investigation was both modest and pharmacologically induced. Gulati *et al.,* (1996) correlated the average systolic velocity at six sites of the mitral annulus with ejection fraction. Although the correlation was good, it did not improve significantly when the six - site average was expressed relative to heart rate, again suggesting that heart rate does not affect the peak velocity of the annulus. However, as all the measurements were taken at rest it is likely once again that there were only modest differences in heart rate between subjects and the conclusion that heart rate does not affect annular velocity should be made with caution.

Few investigators have examined the effect of changes in afterload alone on mitral annular systolic and diastolic velocities. Oki *et al.,* (1999) examined the effect of an acute increase in afterload via an angiotensin II infusion sufficient to bring about an increase of 30 % in MAP. The infusion increased end systolic wall stress and end systolic dimension. This resulted in a significant reduction in peak long axis systolic descent velocity, which is seen during the isovolumetric contraction phase. Early long axis relaxation rates were also reduced but there were no change in the long axis relaxation associated with atrial systole. This is a useful model to investigate the effects of increased afterload, and suggests that the reduction in annular dynamics seen at rest in hypertensives for example (Bruch *et al.,* 1999) may be reversible following anti - hypertensive therapy. However, it is unlikely to represent other situations of

increased afterload, as the systemic release of ionotropic hormones that accompanies exercise for example is absent from this model, and the ability of those ionotropic agents to counter reductions in long axis function cannot be taken into account. There is also evidence that these agents may also be lusitropic and enhance early relaxation rates. (Walsh *et al.*, 1990).

2.10 Effects of Age on Long Axis Function

As mentioned previously, some investigators have attempted to define boundaries for normal systolic long axis function (Gulati *et al.*, 1996; Alam *et al.*, 2000). However, if these suggested parameters are to be used it is important to account for confounding variables such as age. Onose *et al.*, (1999) examined the effect of aging on systolic long axis function in apparently healthy subjects. The cohort ranged from 15 - 78 years of age, and long axis measures were correlated with age, ejection fraction, fractional shortening and the peak dP / dt. The results demonstrated that systolic longitudinal shortening was significantly negatively correlated with age, indicating an impairment of the longitudinal fibre systolic function with increasing age. However, global pump function and contractility as measured across the short axis appeared to be maintained. This is in support of the work done by Alam *et al.*, (1999), who examined both mitral and tricuspid annular movements in a cohort of healthy subjects aged between 22 – 82 years. The cohort was stratified into under 40 years, 40 - 59 years and 60 + years. There was a significant difference in the systolic mitral annular descent velocities between the oldest and youngest group, and a correlation of the

entire cohort identified a significant correlation between age and systolic mitral annular velocity ($r = -0.43$ $p < 0.001$). In addition, Alam *et al.*, (1999) also correlated early diastolic descent velocities, and once again, the mean descent velocity of the oldest group was significantly lower than that of the youngest group. Also there was a more powerful correlation between early relaxation velocities (E_{TDE}) and ageing ($r = -0.81$ $p < 0.001$). This suggests that there is a progressive age related decline in both the systolic contraction and early diastolic relaxation velocities of these longitudinal fibres. Yamada *et al.*, (1999) examined the effect of aging on diastolic long axis function only, in healthy individuals. The results demonstrated a significant inverse correlation between age and long axis early diastolic E_{TDE} velocities at both the septal ($r = -0.61$, $p < 0.05$) and inferior ($r = 0.59$, $p < 0.05$) sites. They also demonstrated a significant age related increase in the ventricular lengthening during atrial systole (A_{TDE} , $r = 0.59$, $p < 0.05$ and $r = 0.57$, $p < 0.05$ for inferior and posterior sites respectively). The significance of this is that whilst the data agrees with other studies with respect to age related decline of systolic and early diastolic function, it also demonstrates an age related increase in atrial component of diastolic filling probably in compensation for the decline in early diastolic relaxation rate. Additionally, as in other reports, they documented that the time from aortic valve closure to peak diastolic E_{TDE} velocity increased as a function of aging, indicating a reduction in the relaxation rate of the long axis.

2.11 Potential Mechanisms For Reduced Long Axis Function in Disease

It is evident that the current literature clearly identifies a reduction both of long axis shortening and lengthening in a variety of pathological states. The precise mechanisms that underlie the reduced long axis function however, is less clear.

2.11.1 Myocyte Disarray

In studies that focused on HCM or DCM patients, one of the reasons for reduced long axis dynamics could be the presence of myocyte disarray. Kim *et al.,* (2000) examined the effect of a familial HCM miss - sense mutation in mice myocytes and compared them to wild type cells. The mice with the mutation had a greater percentage of type III myocytes (irregular shape, disorientated myofibrils). In addition, under artificial stimulation the type III cells demonstrated a reduced end diastolic length and reduced contraction velocity and an increase in the decay time for the Ca^{2+} signal despite similar Ca^{2+} ATPase levels. If these myocytes were expressed in those cells responsible for longitudinal changes then it is evident that reductions in systolic and diastolic velocities are a possibility. Furthermore Usuki *et al.,* (1989) demonstrated a significant inverse correlation between echocardiographically determined percentage wall thickening and the percentage of disarrayed myofibres of the ventricular septum determined post mortem. This again indicates that myofibres in disarray contribute to reduced systolic function.

2.11.2 SUB - ENDOCARDIAL FIBROSIS

Fibrosis of the sub - endocardium may also contribute to the reduced systolic and diastolic function along the long axis. Tazelaar *et al.*, (1987) demonstrated that there was an increased fibrosis in samples from septal myoectomies in patients with HCM and later Varna *et al.*, (2000) demonstrated a correlation between the degree of ventricular hypertrophy and the quantity of fibrosis in patients with HCM. Usuki *et al.*, (1989) also demonstrated a reduction in ventricular contractile function in response to increased myocardial fibrosis. Tazelaar *et al.*, (1987) also identified fibrous sub - endocardial plaques on the septal wall in patients with asymmetric HCM. This was also confirmed from endocardial biopsy examination by Litovisky & Rose (1998).

Hypertensive hypertrophic heart disease has also been shown to contribute to the development of fibrosis. Pick *et al.*, (1989) demonstrated in primates that induction of pressure overload hypertrophy resulted in increased cell necrosis and replacement fibrosis. Huysman *et al.*, (1989) identified an increase in the percentage of microscopic scar tissue, only in the endocardial portion of the heart wall in response to chronic hypertension. In addition, the presence of scar tissue on the endocardial border was increased in subjects with systemic hypertension and coronary artery disease. Therefore, hypertrophy of the left ventricle in response to hypertension has the potential to become evident in the dynamics of the longitudinally contracting fibres of the sub - endocardium before global function is reduced. Hypertensive heart disease has also been shown to result in increased extra cellular collagen content (Pick *et al.*, 1989, Huysman 1989). This increase may result in reduced ventricular compliance

and therefore reduced relaxation velocities. What is currently not known is whether the diffuse ventricular changes that appear in hypertrophy secondary to hypertension will result in reduced long axis function at all sites of the mitral annulus and if HCM causes regional changes in long axis velocities. If this is the case then long axis descent velocities may by useful in the differential diagnosis of hypertension and HCM.

2.11.3 ALTERED Ca^{2+} METABOLISM

Myocyte Ca^{2+} metabolism has been demonstrated to be augmented in a variety of pathologies. Whilst the literature is equivocal on the effect of left ventricular hypertrophy on the abundance of L type Ca^{2+} channels, (responsible for calcium influx through the cell membrane), with studies documenting either no change (Ryder *et al.*, 1993; Delbridge *et al.*, 1997) increased (Kleinman *et al.*, 1988), or decreased (Ming *et al.*, 1994) L - type Ca^{2+} channel abundance in response to hypertrophy. The available data suggests that in all pathological hypertrophic states there is a reduction in the L - type channel response to beta - adrenergic stimulation (Mukherjee and Spinale 1998). Thus for a given level of Ca^{2+} inflow through L - type channels, a higher degree of Beta - adrenergic stimulation is required. Since Ca^{2+} influx through these channels acts as the main excitation contraction coupling system in myocytes and initiates Ca^{2+} release from the sarcoplasmic reticulum (SR). The reduced channel activation at least in basal states due to reduced beta - adrenergic sensitivity will cause a reduced Ca^{2+} release from the SR and hence a reduced contractile response

(Mukherjee & Spinale, 1998). The reduction in beta - adrenergic sensitivity may also be the reason for reduction in longitudinal function with age, as this is associated with a general decline in beta - adrenergic sensitivity (Lakatta, 2000)

Furthermore, the SR of hypertrophied cardiac myocytes has been demonstrated to augment Ca^{2+} control. Ohkusa *et al.,* (1997) demonstrated that in early onset LVH in response to aortic banding in rats, there is an increase in the Ca^{2+} release and uptake and in the number of ryadine binding sites of the SR (responsible for Ca^{2+} release from the SR) indicating an adaptive process. However, after 8 weeks of induced hypertension the changes in SR function were receding. The authors concluded this was indicative of an inability of the myocytes to maintain this adaptation in response to chronic pressure overload. Similarly Arai *et al.,* (1996) demonstrated that mild hypertrophy of rat hearts resulted in a small increase in the concentration of ryadine binding sites and SR Ca^{2+} ATPase and in the mRNA coding for the SRCa^{2+} ATPase. Indicating changes in both Ca^{2+} release and uptake at the molecular level in order to maintain normal function. However, as the degree of hypertrophy progressed the concentrations of ryadine binding sites SRCa^{2+} ATPase and mRNA for the SR Ca^{2+} ATPase were diminished with respect to control hearts. Buttrick *et al.,* (1994) examined the effect of LVH induced by either hypertension, swimming or both. They demonstrated an increase in mRNA for SRCa^{2+} ATPase and troponin I in rats with swimming induced hypertrophy and a reduction in these factors in those with induced reno - vascular hypertension. These findings have recently been found duplicated in human hearts Schotten *et al.,* (1999) examined the concentrations of mRNA encoding

SR Ca^{2+} ATPase in samples from patients with either primary or secondary left ventricular hypertrophy. They demonstrated that compared to controls both types of disease demonstrated reduced mRNA, and a significant negative correlation was found between the degree of mRNA reduction and the degree of hypertrophy of the original ventricle. The authors conclude that the reduced production of SR Ca^{2+} ATPase is an adaptive response unrelated to the aetiology of the disease, but related to severity of hypertrophy, additionally they may explain why changes in diastolic function precede those of systolic function.

While these results are interesting and may well elucidate the mechanisms behind the reductions in the systolic and diastolic velocities of the long axis, they raise a further question. Since long axis function reductions have been shown to precede reductions in global systolic or diastolic function (Gulati *et al.,* 1999; Nagueh *et al.,* 1999), it is unclear why any of these adaptations would occur primarily in the fibres of the sub - endocardium. Furthermore, there are currently no studies examining any of the molecular determinants of myocyte function mentioned above in relation to ventricular transmural depth.

2.11.5 ISCHAEMIA

Several investigators have demonstrated that the sub - endocardium is the largest contributor to wall thickening during systole. These reports suggest a contribution of between 58 % (Myers *et al.,* 1986) to 83 % (Gallagher *et al.,* 1982). Although these

investigations did not directly measure the contribution only from the layers solely responsible for longitudinal shortening it is evident that the deeper the myocardial layer the greater the contribution to wall thickening. Therefore, in basal conditions the vascular tone of the microvasculature of the sub - endocardium is lower and thus coronary reserve is lower in this due to greater oxygen demand at baseline conditions (Colonna *et al.*, 1999). It follows then that in ischaemic conditions the sub - endocardium is the first vulnerable layer (Colanna *et al.*, 1999). Sub - endocardial dyskinesis has been demonstrated in animals when the blood flow reduction has been insufficient to cause any disruption to sub - epicardial or epicardial layers (Colonna 1999). Increased LVM is associated with increased risk of ischaemia of the sub - endocardium both in hypertensive LVH due to thickening of the coronary arteries causing perfusion abnormalities (Gavin *et al.*, 1998), and in cardiomyopathy due to insufficient angiogenesis and mitochondrial destruction (Shrinkathan *et al.*, 1996). One potential mechanism is that sub - endocardial sub - clinical ischaemia secondary to increased ventricular wall mass of pathological origin may result in reductions in sub - endocardial dynamics. However, this is speculative and more studies are required for definite conclusions to be made.

2.12 Summary and Rationale

It is evident from the literature, that reductions in the dynamics of the long axis, which is governed by the fibres of the sub - endocardium, are reduced in a variety of diseases. This is indicative of reduced long axis dynamics being a generalised adaptation to a

pathological process. However, regional variations may occur between different types of diseases, particularly with reference to areas of infarcts. It is also evident that long axis movement can accurately predict global cardiac function both in healthy and diseased subjects, and is of particular use in the identification of normal from pseudo - normal diastolic filling patterns in pathological states resulting from increases in left atrial filling pressure. Furthermore, in healthy subjects there appears to be an age related decline in both systolic and diastolic longitudinal function. Which in turn means that any future studies should use aged matched groups. The apparent independence of long axis movement to loading conditions and the relative ease of measurement with new echocardiographic technology makes it a useful and reliable measure when assessing cardiac function.

It is evident that there are still many gaps in the literature that need to be filled. There are currently no studies in the literature that examine the affect of physiological hypertrophy on longitudinal motion. It is unknown whether exercise training increases the velocities of either systolic or diastolic motion. Indeed, it is unknown if physiological hypertrophy reduces long axis function. Cardiogenic stretch reflexes for example are always reduced in hypertrophied hearts whether pathological or physiological in origin (Gianattsio 1989). In addition if exercise training does affect long axis velocities it may be of use in the differentiation of pathological and physiological hypertrophy. Furthermore, it is unknown whether exercise training can reduce or prevent the apparent age related decline in longitudinal dynamics. Finally, it

is unknown whether the type of exercise training that created the physiologically hypertrophied heart has a differential affect on longitudinal motion.

The purpose of this study is to examine the effects of both pathological and physiological hypertrophy on longitudinal dynamics, measured via TDE assessment of mitral annular movement and compare them to controls. The affect of ageing in athletic populations will also be examined by comparing in senior athletes with controls and pathological patients.

2.13 HYPOTHESES

To account for the fact that measurements of longitudinal function are composed of more than one aspect (systolic velocity, E_{TDE} and A_{TDE}), each hypothesis is assigned a number, with sub components of long axis function assigned A, B or C respectively.

H 1. Younger athletes with physiological LVH induced by endurance training are not different to younger subjects with pathological LVH in either:

A - Long axis systolic function.

B - Long axis E_{TDE} function.

C – Long axis A_{TDE} function.

H 2. Younger athletes with physiological LVH induced by resistance training are not different to younger subjects with pathological LVH in either:

A - Long axis systolic function.

B - Long axis E_{TDE} function.

C – Long axis A_{TDE} function.

H 3. Older athletes with physiological LVH induced by endurance training are not different to older subjects with pathological LVH in either:

A - Long axis systolic function.

B - Long axis E_{TDE} function.

C – Long axis A_{TDE} function.

H 4. Older athletes with physiological LVH induced by endurance training are not different to older subjects with pathological LVH in either:

A - Long axis systolic function.

B - Long axis E_{TDE} function.

C – Long axis A_{TDE} function.

H 5. Long term endurance training does not prevent the normal age related decline in:

A – Long axis systolic function.

B – Long axis E_{TDE} function.

C – Long axis A_{TDE} function.

H 6. Long term resistance training does not prevent the normal age related decline of:

A – Long axis systolic function.

B – Long axis E_{TDE} function.

C – Long axis A_{TDE} function.

H 7. Immediately following $\dot{V}O_{2PEAK}$ there is no difference between endurance trained athletes and controls in terms of their:

A – Long axis systolic function.

B – Long axis E_{TDE} function.

C – Long axis A_{TDE} function.

H 8. Immediately following $\dot{V}O_{2PEAK}$ there is no difference between resistance trained athletes and controls in terms of their:

A – Long axis systolic function.

B – Long axis E_{TDE} function.

C – Long axis A_{TDE} function.

H 9. There is no relation between VO_{2PEAK} and either:

A – Long axis systolic function.

B – Long axis E_{TDE}.

C – Long axis A_{TDE}.

CHAPTER 3: A COMPARISON OF LONG AXIS FUNCTION AT REST IN YOUNG SUBJECTS WITH PATHOLOGICAL OR PHYSIOLOGICAL HYPERTROPHY WITH NORMAL CONTROLS

3.1 ABSTRACT

The cardiac cycle cause longitudinal fibres, located in the sub - endocardium, to oscillate the mitral valve during systole and diastole. Such movements of the mitral annulus are referred to as long axis function. To identify echocardiographic indices of long axis function that may differentiate between pathological and physiological left ventricular LV hypertrophy, 60 subjects with different types of LVH were compared, 15 patients with hypertrophic cardiomyopathy (HCM), 15 patients with systemic hypertension (HT), 15 weightlifters (WL), 15 runners (R) and 15 normal subjects (C). All subjects were aged between 20 - 36 years. Standard echocardiographic procedures were performed including measurement of left ventricular mass (LVM), ejection fraction (EF), and Doppler measurements of blood flow in early diastole (E) and atrial systole (A). In addition using tissue Doppler echocardiography (TDE) systolic, early diastolic (E_{TDE}) and atrial systolic (A_{TDE}) velocities of mitral annulus were measured. TDE assessment of mitral movement was performed at four sites on the annulus, lateral, medial inferior and anterior segments. There were no differences in mean age or global ejection fraction between groups. HCM and HT had lower average long axis systolic and E_{TDE} velocities than either athletes or controls, (Systole 7.2 ± 1.2. 7.6 ± 1.8, 10.8 ± 1.7, 10.6 ± 2.1, 11.0 ± 0.2 for HCM, HT, WL, C and R respectively $p < 0.01$, E_{TDE} 7.0 ± 3.2, 7.3 ± 2.5, 12.2 ± 3.1, 12.4 ± 3.3 14.2 ± 3.5 for HCM, HT, WL, C and R respectively, $p < 0.01$ for both variables for diseased groups versus controls or either athletic groups) The best differentiation of pathological from physiological hypertrophy was provided by a mean early diastolic annular velocity 11 cm s^{-1} (sensitivity 100 %, specificity 90 %). Thus long axis systolic and early diastolic velocities are decreased in patients with pathological hypertrophy, but preserved in athletes. These simple new echocardiographic measures can differentiate between pathological and physiological hypertrophy.

3.2 INTRODUCTION

Experimental and autopsy data demonstrate that pathological left ventricular (LV) hypertrophy is associated with myocardial fibrosis, particularly in the sub - endocardium (Pearlman *et al.*, 1982; Pick *et al.*, 1989; Huysman *et al.*, 1989). Thus, patients with pathological hypertrophy may have sub - endocardial dysfunction, even when global LV function is normal. There are two major myocardial layers: fibres in the sub - epicardial layer are orientated circumferentially and mainly responsible for short axis movement, while those in the sub - endocardium are aligned longitudinally from apex to base, and responsible for long axis dynamics (Greenbaum *et al.*, 1981). Longitudinal contraction results in apical displacement of the mitral annulus (Jones *et al.*, 1990), which is therefore an echocardiographic marker of sub - endocardial function. Mitral annular velocities can now be quantified using pulsed wave tissue Doppler (Isaaz *et al.*, 1993).

This study was designed to test the hypotheses that an assessment of longitudinal function by tissue Doppler measurement of mitral annular motion will provide an echocardiographic criterion that can differentiate between physiological and pathological LVH in subjects under 35 years of age.

3.3 METHODS

3.3.1 SUBJECTS

15 patients with mild obstructive hypertrophic cardiomyopathy (HCM), 15 patients with LVH secondary to systemic hypertension (HT), 15 weightlifters (WL) 15 long distance runners (R) and a control group (C) of 15 sedentary subjects were enrolled into the study. The protocol was approved by the local ethics research committee and each subject gave written informed consent.

The inclusion criteria for pathological LVH were:

1) HCM : unexplained LVH (septal thickness ≥ 13 mm), presence of systolic anterior movement of the anterior mitral leaflet and / or sub valvular apparatus, and resting intra ventricular systolic gradient > 10 mm Hg (21 ± 7 mm Hg). 50 % of subjects demonstrated aymetric LVH (IVS : Posterior wall ratio > 1.3)

2) Patients with systemic hypertension: resting diastolic blood pressure ≥ 100 mm Hg before treatment, and increased LV mass index (LVMi) (> 131g m^{-2} Devereaux *et al.*, 1987).

Only patients between 20 - 35 yrs were included (Table 3.1). Patients with valve disease, coronary artery disease, conduction disturbances, a dilated ventricle (end -

systolic diameter index > 25 mm m^{-2}), and / or a decreased ejection fraction (< 50 %), were excluded. All patients were in sinus rhythm. Beta - blockers and calcium channel antagonists, were stopped 24 hours before the study.

Athletes were included if they had an increased LVM index (> 131 g m^{-2} Devereaux 1987). Each participant had trained for at least 10 hours / week (aerobic or resistance exercise), for the last 5 years. (11 ± 2hrs week for 9 ± 5 years), and athletes were split into two groups:

15 strength trained athletes (weightlifters) and 15 endurance trained athletes (long distance runners). 7 of the weightlifters admitted to using anabolic steroids for between 2 - 12 months whilst training. All athletes were normotensive, non - smokers with normal blood glucose and lipid profiles. All subjects were instructed to abstain from caffeine and physical exercise for at least 24 hours prior to the examination.

3.3.2 ECHOCARDIOGRAPHY

Studies were performed with a commercially available ultrasound system equipped with tissue Doppler capabilities (Vingmed system 5), using a 2.5MHz transducer in conjunction with an electrocardiogram. Heart rate and blood pressure were measured following 15 minutes of rest. At least 5 consecutive beats in each view were recorded on VHS video tape, during passive held end - expiration. All measurements were the mean of 3 consecutive beats. All measures and calculations were perfomed by the same experienced investigator.

3.3.3 STANDARD ECHOCARDIOGRAPHIC STUDIES

In accordance with the American Society of Echocardiography (ASE) guidelines (Schiller *et al.*, 1989) M - mode tracing from the parasternal long axis view were used to measure diameters of the aortic root (Ao), left atrium (La), end - diastolic diameter of the right ventricle (EDDr), septal thickness (IVS), LV diameter (LVD), and posterior wall thickness (PW) in systole and diastole. 2D mode frontal plane images were recorded from the apical view for measurement of end - diastolic (EDA) and end - systolic areas (ESA), and LV cavity length. Pulsed - wave Doppler of transmitral flow, was used to assess global diastolic function. The sample volume was placed at the tips of the mitral leaflets, in the apical 4 - chamber view. The Doppler indices from the velocity time integral were; peak early diastolic (E) and peak atrial systolic (A) blood flow velocities. E - wave deceleration time, (the time interval between peak E velocity and the onset of atrial systole) and isovolumetric relaxation time (the time between the second heart sound (aortic valve closure) and the onset of early diastolic filling). E / A ratio was also calculated. LV inflow was recorded by colour M - mode echocardiography and flow propagation velocity was measured (Brun *et al.*, 1992).

3.3.4 ECHOCARDIOGRAPHIC DATA ANALYSIS

Analysis was performed off line for the calculation of LV volumes, ejection fraction (EF), end systolic wall stress (ESWS), and LVM. Ejection fraction was calculated as End diastolic volume (EDV) minus end systolic volume (ESV). Volumes were calculated by the modified Simpsons bi - plane method, utilising orthogonal apical two

chamber and short axis four chamber views, again in accordance with ASE guidelines (Schiller *et al.*, 1989). ESWS in 10^3 Dynews cm^{-2} , was calculated according to the formula: ESWS = 0.334 (P)(d) / h [1 + (h / d) were P is systolic pressure, h is systolic posterior wall thickness, d is systolic left ventricular diameter, (Grossman *et al.*, 1975). LV mass was estimated using LVM = (1.05 x [(EDD + PWTd + IVSTd)^3 - EDD^3] - 13.6), were EDD is the end diastolic dimension, PWTd is the posterior wall thickness at the end of diastole and IVSTd is the interventricular septal thickness at the end of diastole (Devereaux 1987). Volumes and mass were indexed by body surface area.

3.3.5 Long Axis Function by Tissue Doppler

Longitudinal movements of the mitral annulus were measured at four sites on the annular ring using tissue Doppler echocardiography. Four areas investigated were the lateral site, the most lateral border of the annular ring; medial site, were the annulus inserts into the IVS; the anterior site was the insertion of the annulus into the anterior wall of the ventricle and inferior site being the insertion of the annulus into the posterior wall of the ventricle. In all cases the placement of the sample volume (gate 6 mm) was guided using 2D cross sectional images followed by colour M - mode traces in order to improve endocardial boundary definition. As with all Doppler measurements care was taken to ensure the angle of incidence was as close to 0^o compared to the line of action of the musculature. For measurement of the lateral and medial sites, traces were taken using the apical four chamber view to guide the cursor, while for the anterior and inferior apical 2 chamber views were utilised. From the time

velocity integral traces generated, peak systolic velocity was measured, this excluded velocities measured during the isovolumetric contraction phase. Peak early diastolic (E_{TDE}) and atrial systolic (A_{TDE}) velocities of the annulus were also measured. From this E_{TDE} / A_{TDE} ratio could also be assessed. In order to generate a measure of overall long axis function the average of all four sites for systolic, E_{TDE} and A_{TDE} was also calculated. The heterogeneity index assessed the degree of similarity of systolic descent velocities between annular sites, it is defined as the absolute difference between peak systolic velocities at each site and their mean.

$$\text{Heterogeneity Index} = ([M - \text{Mean}] + [L - \text{Mean}] + [I - \text{Mean}] + [A - \text{Mean}]) / 4.$$

3.3.6 SHORT AXIS FUNCTION BY TISSUE DOPPLER

Short axis function was also assessed using tissue Doppler techniques, this allowed for assessment of short axis function (i.e. the myocardial velocities occurring at 90° to the long axis). In this investigation short axis velocities were investigated at two sites, the IVS and posterior wall. Measurements were taken using the parasternal short axis two chamber view for the posterior wall and the parasternal four chamber, long axis view for the IVS. As subepicardial fibres govern short axis function the sample volume was placed level with the mitral leaflets but in mid myocardium for IVS measurements of short axis, and above the insertion of papillary muscle but again in mid myocardium for posterior wall assessment. Again the plscement of the sample volume was guided using the 2D image and the angle of incidence between the muscle line of action and

the incident ultrasound beam was kept as close to 0° as possible. From the generated time velocity integrals peak short axis systolic velocity (again excluding velocities of the isovolumetric contraction phase) were measured. Peak E_{TDE} and A_{TDE} were also measured for the short axis and hence short axis E_{TDE} / A_{TDE} ratio was calculated..

3.3.7 REPRODUCIBILITY

Paired recordings obtained from 10 subjects were analysed to determine the reproducibility of both acquiring and measuring myocardial velocities recorded by tissue Doppler echocardiography. To assess intraobserver variability, the same observer recorded and measured the data twice, from the same patients. Data was analysed using systolic and diastolic velocities measured from the lateral, medial, posterior and inferior sites on the mitral annulus. The reproducibility of annular velocities averaged from all 4 sites were also assessed

3.3.8 STATISTICAL ANALYSIS

Statistical analysis was performed using the SPSS software package (v 9.0). Results are presented as mean value ± SD. Differences between groups were considered using analysis of variance (ANOVA), with subgroup analysis by the Scheffe F test. Sensitivity, specificity and accuracy were assessed in the standard manner (Greenhalgh 1997). Multiple forward stepwise binomial logistic regression was used to define the best association of variables that can differentiate between pathological and physiological hypertrophy. A $p < 0.05$ was considered significant for a 2 tailed test.

Reproducibility of measuring peak systolic velocities of ventricular septum, posterior wall and annulus was determined in 6 subjects according to the methodology previously reported (Vinereanu *et al.,* 1999).

3.4 RESULTS

General characteristics of the cohort are presented in Table 3.1. Standard echocardiographic data are presented in Table 3.2.

Table 3.1 Subjects characteristics for study 1

	AGE (Yrs)	*BSA (m^2)*	*HR (bpm)*	*BPS (mm Hg)*	*BPD (mm Hg)*
HCM	27 ± 6	1.9 ± 0.3	66 ±9	127 ± 8	79 ± 8
Hypertensive	34 ± 1	1.8 ± 0.2	69 ± 9	168 ± 18	108 ± 12
Weightlifters	30 ± 3	2.1 ± 0.2	72 ± 11	131 ± 9	80 ± 8
Controls	30 ± 6.	1.9 ± 0.15	68 ± 11	126 ± 10	76 ± 6
Runner	30 ± 4	1.9 ± 0.17	61 ± 9	125 ± 12	76 ± 7

BSA = body surface area, HR = heart rate, BPS = systolic blood pressure, BPD = diastolic blood pressure. Values are mean ± SD

3.4.1 LONG AXIS FUNCTION

Patients with HCM and HT had lower long axis systolic and early diastolic velocities than either runners weightlifters or controls at all 4 sites of the mitral annulus ($p < 0.05$; Figure 3.4, 3.5) late diastolic velocities (A_{TDE}) were not different. 4 site average systolic descent velocities were therefore reduced in both patient groups compared to healthy groups ($p < 0.01$; Figure 3.1). Also 4 site average early diastolic ascent velocities were also reduced in patient groups ($p < 0.01$; Figure 3.1). In addition the early diastolic ascent velocities of the runners was also greater than either the controls or the weightlifters ($p < 0.01$; Figure 3.1)

Patients with asymmetric septal hypertrophy (ventricular / posterior wall diastolic thickness ratio $\geq$ 1.3) had lower peak systolic velocities for the medial and inferior sites of the mitral valve than patients with concentric hypertrophy : 7.0 $\pm$1.6 versus 7.9 $\pm$ 1.0 cm s^{-1}, and 7.7 $\pm$ 2.1 versus 8.7 $\pm$ 1.0 cm s^{-1} respectively ($p < 0.05$). The estimated left atrial filling pressure was also significantly higher in both groups with pathological LVH. In addition 80 % of the pooled pathological LVH subjects displayed apparently normal E / A ratio, while 90 % displayed an abnormal E_{TDE} / A_{TDE} ratio (i.e. < 1; Table 3.2).

Table 3.2 Standard echocardiographic findings for each group.

	HCM	*HT*	*WL*	*Control*	*Runners*
Aortic Outflow (mm)	33 ± 6	33 ± 3	35 ± 3	34 ± 2	30 ± 3
Left .Atrium. (mm)	39 ± 8	39 ± 3	40 ± 4	35 ± 4	40 ± 5
Right Ventricle. (mm)	20 ± 5[1]	25 ± 2	26 ± 3	20 ± 2[13]	25 ± 3
Septum (mm)	17 ± 2[4132]	13 ± 1.6[2]	13 ±. 9[2]	10 ± 1	12 ± 1.7
EDD (mm)	45 ± 8[13]	48 ± 5	56 ± 5	51 ± 3.6	56 ± 4
PW (mm)	13 ± 2[2]	13 ± 1.3[2]	12 ± 1.6[2]	8 ± 1.2	11 ± 2[2]
ESD (mm)	28 ± 7[1]	26 ± 6[1]	38 ± 4.6	30 ± 2.5[1]	34 ± 4
(IVS + PW) / EDD	0.7 ± 0.1[1234]	0.6 ± .1[2]	0.4 ±0.16	0.4 ± 0.1	.4 ± 0.1
Septum / PW	1.3 ±0.3	1.0 ± .02	1.1 ± 0.2	1.2 ± 0.2	1.0 ±0.1 3
EF (%)	63 ± 6	65 ± 9	63 ± 5.8	68 ± 6.8	59 ± 5
ESWS (10^3 Dynes cm^{-2})	36 ± 9	44 ± 23	61 ± 15	55 ± 13	60 ± 30
LVMI (g m^{-2})	188 ± 45[2]	166 ± 23[2]	181 ± 34[2]	105 ± 16	171 ± 31[2]
Mitral E (cm s^{-1})	65 ± 14	83 ± 10	74 ± 19	84 ± 11	87 ± 16
Mitral A (cm s^{-1})	46 ± 5	68 ± 10	60 ± 19	57 ± 11	48 ± 12
Mitral E / A	1.4 ± 0.3	1.2 ± 0.4	1.3 ± 0.3	1.5 ± 0.3	1.8 ± 0.3[1]
E Dt (ms)	185 ± 24	180 ± 32	174 ± 28	174 ± 34	213 ± 39
IVRT (ms)	118 ± 28	85 ± 31	91 ± 150	80 ± 15	105 ± 16
FPV (cm s^{-1})	56 ± 9	52 ± 9	51 ± 8	50 ± 10	62 ± 11

[1]Denotes significantly different from Weightlifters, [2] denotes significantly different from controls, [3] denotes significantly different from Runners and [4] denotes significant difference to hypertensives. EDD = end diastolic dimension; PW = posterior wall; ESD = end systolic dimension; EF = ejection fraction; ESWS = end systolic wall stress; LVMI = left ventricular mass index; E Dt = E wave deceleration time (milli – seconds); IVRT = isovolumetric relaxation time (milli - seconds); FPV = flow propagation velocity. Values are means ± standard deviations

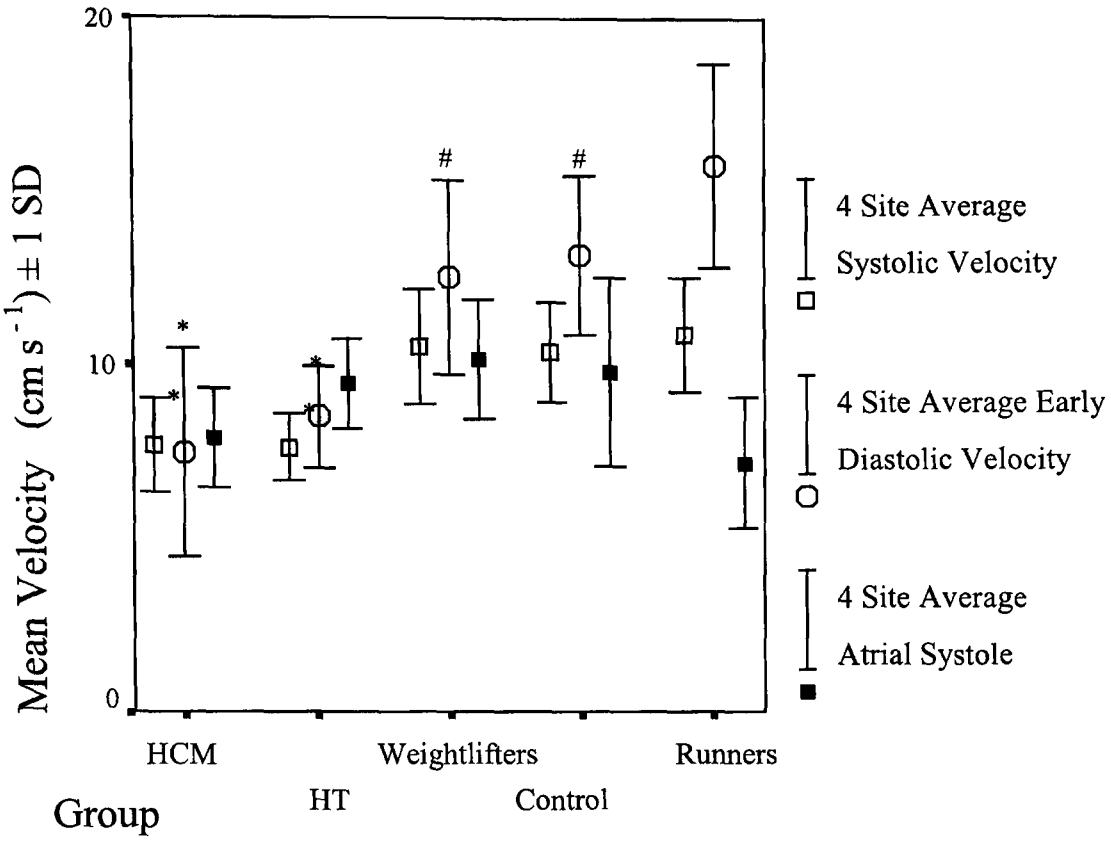

Figure 3.1 Tissue Doppler measurements of the 4 site average for systolic descent and diastolic relaxation velocities. *Denotes significantly different from Weightlifters, Runners and Controls. # denotes significantly different to runners only.

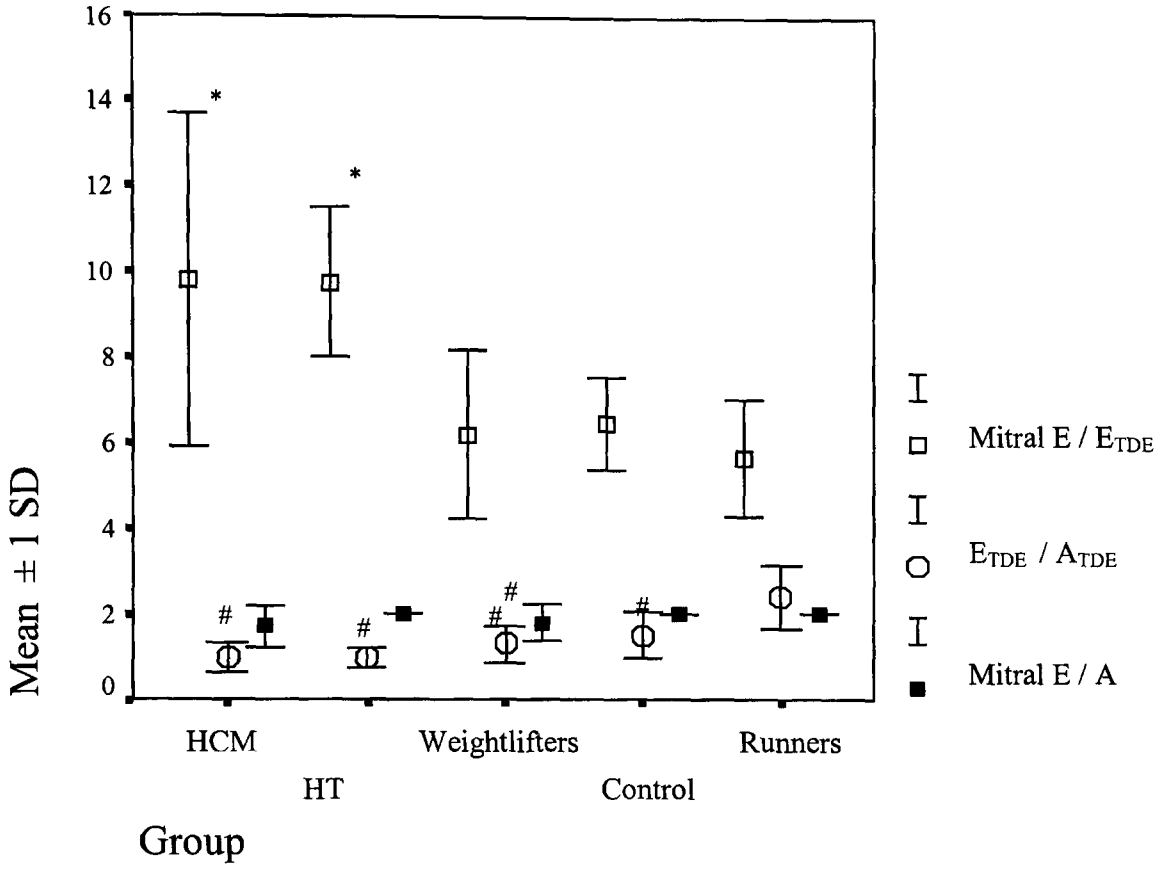

Figure 3.2 E / E_{TDE}, E_{TDE} / A_{TDE} and Mitral inflow E / A ratio's for each group.

* Denotes significantly different from weightlifters, runners and controls, # denotes significantly different from runners only.

Table 3.3 Tissue Doppler echocardiographic values for velocity of shortening and relaxation along the short axis.

Group	*IVS S*	*IVS E_{TDE}*	*IVS A_{TDE}*	*IVS E_{TDE} / A_{TDE}*	*PW S*	*PW E_{TDE}*	*PW.A_{TDE}*	*PW E_{TDE} / A_{TDE}*
HCM	6.0± 2.7	7.0 ± 4.1	4.5 ± 0.8	1.7 ± 0.7	6.8 ± 2.1	9.6 ± 4.6	5.5 ± 1.0	1.8 ± 1.2
Hypertensive	8.2 ± 3.4	7.3 ± 3.1	8.4 ± 5.0	1.1 ± 0.2	7.6 ± 2.0	10.9 ± 3.1	5.9 ± 1.4	1.8 ± 0.9
Weighlifter	6 ± 2.5	6.6 ± 1.9	5.7 ± 2.5	1.2 ± 0.4	7.5 ± 1.8	13.0 ± 4.7	5.2 ± 1.1	2.5 ± 0.7
Controls	5.2 ±1.3	6.7 ± 2.1	5.6 ± 1.8	1.2 ± 0.4	6.8 ± 1.6	12.6 ± 4.5	5.6 ± 2.5	2.4 ± 1.2
Runner	7.0 ± 1.6	7.3 ± 2.3	4.2 ± 1.4	1.8 ± 0.5	8.7 ± 1.6	14.7 ± 3.4	4.3 ± 1.0	3.4 ± 1.0

E_{TDE} = Early diastolic annular velocity, A_{TDE} = Atrial systolic annular velocity, IVS = Inter – ventricular septum ventricular septum; PW = posterior wall; S = systolic velocity; E_{TDE} = early diastolic velocity. All values are in cm s^{1}, except for ratio measures which have no units.

Table 3.4 Performance of echocardiographic findings in the discrimination of pathological and physiological hypertrophy.

	Sensitivity	*Specificity*	*Accuracy*
4 Site Systolic Descent Velocity < 9 cm s^{-1}	80 %	93 %	90 %
4 Site E_{TDE} Velocity < 11 cm s^{-1}	100 %	90 %	92 %
E_{TDE} / A_{TDE} < 1	90 %	87 %	88 %
(IVS + LVPW) / LVEDD > 0.6	73 %	90 %	82 %
Mitral E / A ratio < 1	20 %	82 %	73 %
Mitral E / E_{TDE} < 7	90 %	74 %	70 %
Flow Propagation Velocity < 50 cm s^{-1}	40 %	64 %	56 %

E_{TDE} = Early diastolic annular velocity, A_{TDE} = Atrial systolic annular velocity, IVS = Inter – ventricular septum, LVPW = left ventricular posterior wall, LVEDD = Left ventricular end diastolic dimension, E = blood flow velocity during early diastole, A = blood flow velocity during atrial systole

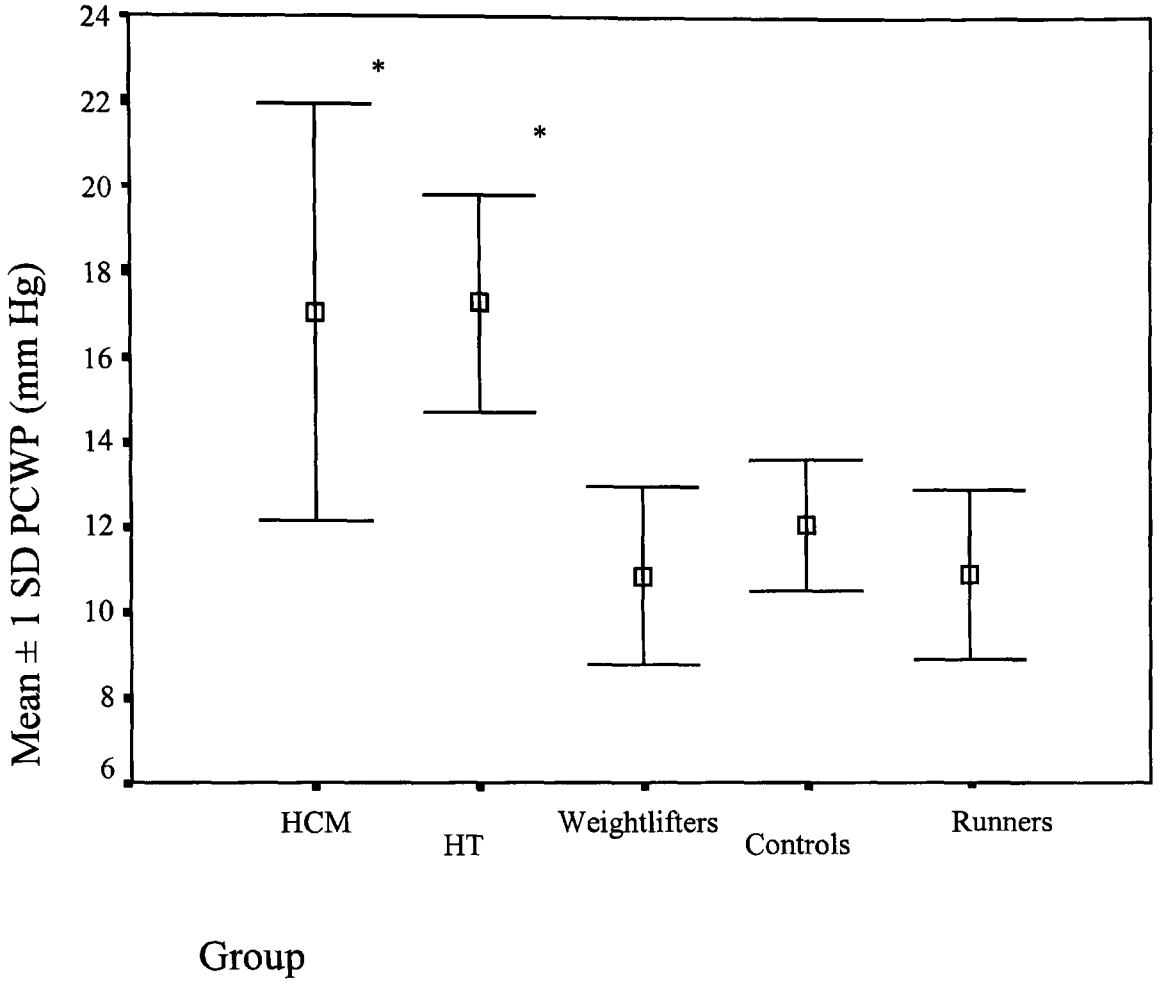

Figure 3.3 Estimated pulmonary capillary wedge pressure (PCWP) from the equation of Sunderswaran *et al,*. (1998). * Denotes significantly different from weightlifters controls and runners.

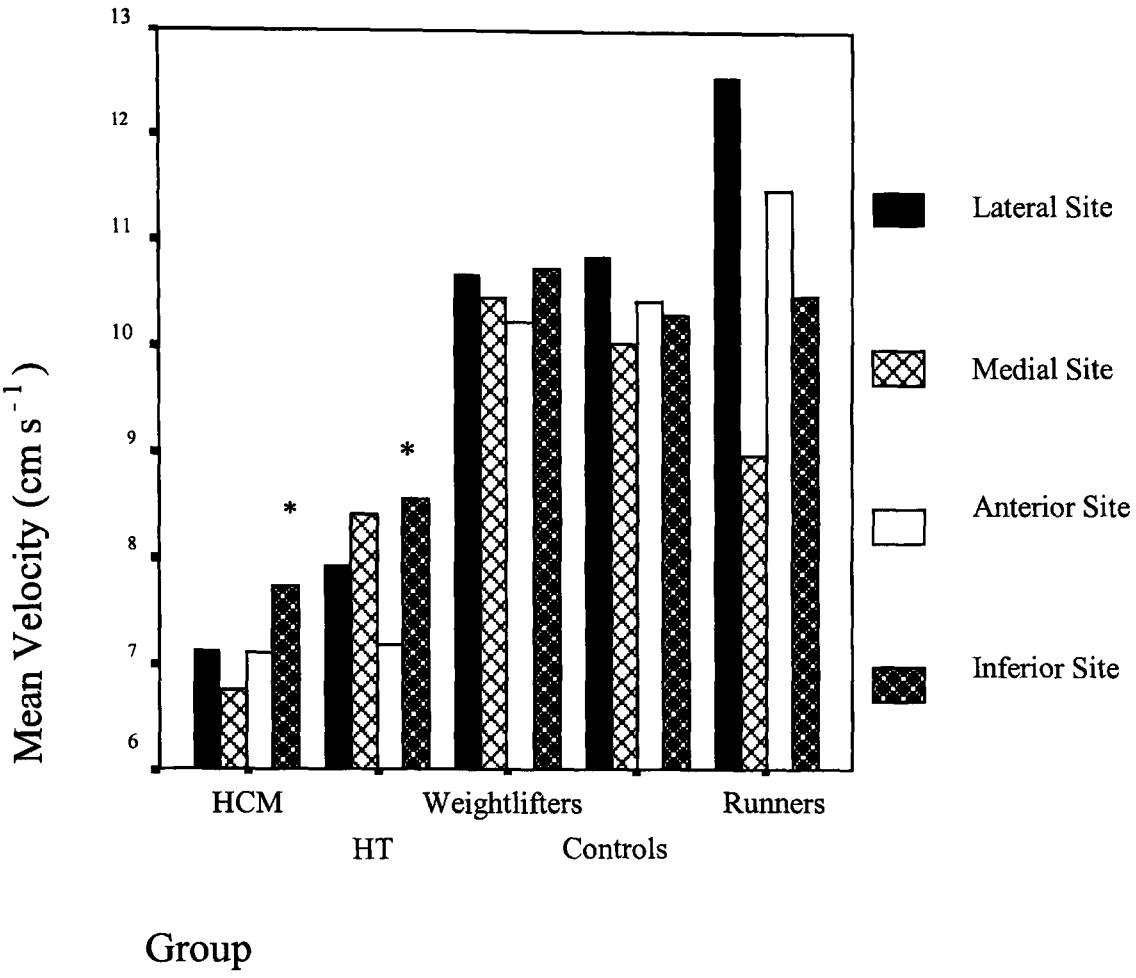

Figure 3.4 Grouped Average systolic descent velocity for each of the annular sites.

* Denotes significantly different at all four sites compared to weightlifters runners and controls.

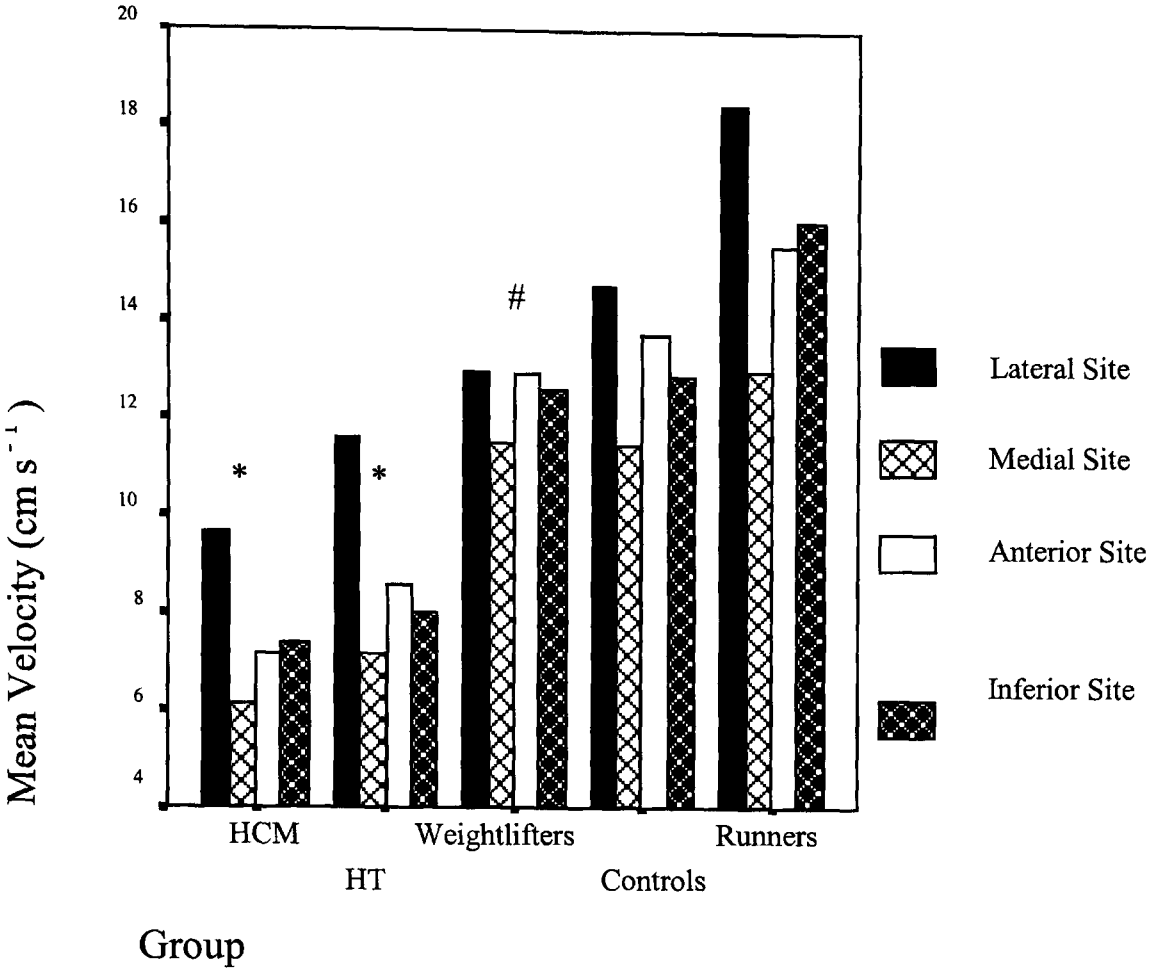

Figure 3.5 Early diastolic relaxation velocities (E_{TDE}) for each of the annular sites.

* Denotes significantly different from Weightlifters controls and runners at each of the four sites. # Denotes significantly different to runners at the lateral site only.

3.4.2 ACCURACY FOR DIFFERENTIATING PHYSIOLOGICAL AND PATHOLOGICAL LVH

By analysis of individual sites (Figure 3.4), the best differentiation between pathological and physiological hypertrophy was provided by a mean systolic anterior annular velocity < 9 cm s^{-1} (Figure 3.4). From conventional echocardiographic parameters, the best accuracy was found for the ratio of (septum + posterior wall) / EDD. Other traditional echocardiographic measures were not different between groups (ejection fraction, fractional shortening, E wave deceleration time, flow propagation velocity, isovolumetric relaxation time, $p > 0.05$ between groups for all variables). Using binary logistic regression, testing all variables from Table 3.4 the best differentiation was provided by association of mean early diastolic annular velocity < 11 cm s^{-1}, and systolic descent velocity of < 9 cm s^{-1}, sensitivity 95 %, specificity 100 % and accuracy 97 %.

The sensitivity, specificity and accuracy of the indices of long axis function alone in comparing physiological hypertrophy and HCM alone was 100 % for sensitivity, specificity and accuracy for both average systolic descent velocity < 9 cm s^{-1}, and $E_{TDE} < 11$ cm s^{-1} . A septal thickness above 15 mm had a sensitivity of 50 %, a specificity of 91 % and an accuracy of 83 % for the diagnosis of HCM, however, septal thickness of 13 mm or above was an inclusion criteria

3.4.3 Short Axis Function by Tissue Doppler

Short axis systolic and diastolic velocities were not different between the groups, either for IVS or PW (Table 3.3)

3.4.4 Heterogeneity Index

Mitral annular systolic velocities were lower in both groups of patients with pathological hypertrophy compared with normal subjects, but they were not different between each other. The heterogeneity index also did not discriminate between pathological groups. (0.75 ± 0.9 cm s^{-1}, in HCM patients v's 0.51 ± 0.6 cm s^{-1}, in patients with hypertension, $p < 0.05$).

3.4.5 Inter Ahlete Comparisons

There were no differences in strength trained weightlifters and endurance athletes for age (Table 3.1) or for global ejection fraction, (61 ± 5.8 % versus 59 ± 5 %). However, the weightlifters recorded a greater body surface area (2.1 ± 0.21 versus 1.96 ± 0.17 m^2 $p < 0.01$). There was no difference in either posterior or septal wall between weightlifters and runners. LVM index was not significantly different (182 ± 38 versus 165 ± 16 g m^{-2}). Short axis and long axis velocities were similar. Runners had better diastolic function, as judged by faster velocities during early diastolic filling. The E / A ratio of mitral inflow was 1.84 ± 0.34 in runners versus 1.29 ± 0.28 in weightlifters ($p < 0.01$). The diastolic long axis velocities gave E_{TDE} / A_{TDE} ratio of 1.34 ± 0.3 v's 2.34 ± 0.76 for weightlifters and runners respectively ($p < 0.01$).

3.4.6 REPRODUCIBILITY

Intra - observer variability was ± 7.0 % for ventricular septum, ± 2.7 % for posterior wall,. The reproducibility at each of the annular sites was ± 2.0 %, ± 1.9 %, ± 1.8 %, and ± 2.5 % respectively for L,M,A, and I sites. The 4 site average was 1.4 % .

3.5 DISCUSSION

The results of this investigation indicate that assessment of resting long axis function by tissue Doppler measurement of mitral annular velocities can differentiate between different types of LV hypertrophy. This may be clinically important because it is sometimes difficult or impossible to determine the significance of hypertrophy using other methods (Dickuth *et al.*, 1994; Maron *et al.*, 1995).

3.5.1 DIFFERENTIATION BETWEEN PATHOLOGICAL AND PHYSIOLOGICAL LVH

A variety of criteria have been proposed to aid the diagnosis of pathological or physiological hypertrophy of the left ventricle these include rest and / or post exercise LV dysfunction (measured by reversal of E / A ratio and / or a prolongation of the E wave deceleration time, (Lewis *et al.*, 1992); an increase in LV wall thickness above 16 mm (Pellicia *et al.*, 1991); a ratio of septum + posterior wall / end diastolic diameter greater than 0.6 (Dickuth *et al.*, 1994) and the ratio of septal / posterior wall above 1.3 (Julian 1992). However, in the present study all these criteria either failed to differentiate between pathological and physiological groups, or had poor sensitivity, specificity and accuracy results (Table 3.4). Subjects with pathological LVH had greater thickness of the ventricular septum than either the weightlifters or the runners; this was an inclusion criteria for the HCM group, thus septal thickness above 15 mm had poor sensitivity but good specificity for the differential diagnosis. The

conventional criteria that differentiated best between pathological and physiological hypertrophy was the ratio of septum + posterior wall / end diastolic diameter, which is in agreement with previous work by Dickuth *et al.*, (1994)

The best single determinant of pathological or physiological hypertrophy was the 4 site average E_{TDE} velocity, and the best combination of factors from the regression analysis was $E_{TDE} < 11$ cm s^{-1} and systolic velocity of < 9 cm s^{-1}. Both these measurements were better differentiators than those outlined above. It is interesting that the best combination of predictor variables were both measurements of longitudinal dynamics. This demonstrates that systolic and diastolic tissue velocities along the long axis can rapidly assess the nature of hypertrophy of the left ventricle. Additionally as the sensitivity, specificity and accuracy of the systolic descent velocity applied to just the HCM and athletes was 100 % and if systolic descent velocity is unchanged by exercise training as appears to be the case in this study, then the criteria determined in this investigation may be useful markers for identifying young athletes with underlying pathologies. Especially as increases in left ventricular mass in the absence of an overt increase in systemic pressure is unlikely to be due to hypertension. This is an intriguing theory as most cases of sudden death in subjects under the age of 35 are due to undiagnosed cardiomyopathy. (Maron *et al.*, 1995). Tissue analysis by ultrasonic videodensitometry (DiBello *et al.*, 1997) or quantitative analysis of backscatter (Lattazni *et al.*, 1992), and the myocardial velocity gradient measured across the posterior wall (Palka *et al.*, 1997) have also been used to distinguish between

pathological and physiological hypertrophy. However, off line analysis and / or non - commercially available software were used in all these methods.

The reductions in systolic and diastolic velocities observed in HCM and hypertensive patients in this study are largely in agreement with other investigations of longitudinal changes in these subject groups (Gulati *et al.*, 1996; Lange *et al.*, 1997; Mishiro *et al.*, 1999; Nagueh *et al.*, 2000; Tabata *et al.*, 2000). Pathological but not exercise induced hypertrophy is associated with sub - endocardial fibrosis, which is one potential mechanism for the eventual failure of the hypertrophied ventricle (Huysman *et al.*, 1989; Frohlich 1999; Vatner *et al.*, 1993). This is the first study to examine the effect of either endurance or resistance training on longitudinal function. There was no difference between the runners, weightlifters and controls with respect to systolic annular descent velocities (Figure 3.1). This is of importance for two reasons. Firstly the groups with physiologically hypertrophied hearts had superior systolic dynamics than the pathologic groups. This suggests that systolic long axis descent velocity is not diminished purely as a function of an increase in LVM. Although prior investigations into pathological hypertrophy have demonstrated reduced systolic function (Mishiro *et al.*, 1999; Nagueh *et al.*, 2000; Tabata *et al.*, 2000) the lack of data regarding physiological hypertrophy meant that a reduction in systolic long axis function due purely to increased cardiac mass could not be ruled out.

Secondly, it also demonstrates that exercise training does not increase resting systolic long axis function, as there is no significant difference between the athletic groups and

controls. This may be due to such a small mass of cardiac tissue being responsible for longitudinal shortening that any increase in systolic function following training would be so small as to be outside the sensitivity of the equipment. Although if that were the case then identification of diastolic differences would not have been expected either. Alternatively, it is possible that exercise training results in an increase in the maximal systolic contraction velocity with no change evident at rest, (i.e. although the value at rest is unchanged, it represents a smaller percentage of the functional reserve of the sub - endocardium). However, why this should be the case when alterations in diastolic function are evident at rest is unclear. It is possible that exercise training simply does not increase systolic long axis function. This is an important point for future clarification, if systolic dynamics are not affected by training then the possibility of identifying athletes with underlying pathology are increased. However, if training does affect the functional reserve of the contracting tissue then there is the possibility that training induced improvements will mask any reductions in function due to pathological processes.

The early diastolic component of long axis function also discriminated between pathological and physiological groups, with HCM and HT demonstrating reduced early diastolic velocities compared to both groups of athletes and controls. Furthermore, the runners demonstrated lower A_{TDE} velocities than the weightlifters, faster E_{TDE} velocities than weightlifters and controls and higher E_{TDE} / A_{TDE} ratios that either weightlifters or controls. The ability of endurance training to improve cardiac performance is well documented (Matsuda *et al.*, 1983). However, this is the first time

specific improvements in diastolic long axis relaxation velocities have been shown. It is likely that the higher E_{TDE} and E_{TDE} / A_{TDE} ratio of the endurance athletes is an adaptation to endurance training. The low A_{TDE} represents a reduced force of atrial contraction at rest. This may indicate a higher functional reserve available during exercise. The preponderance of E_{TDE} relaxation velocities over those of atrial systole indicate that at rest, blood collected in the ventricle during early diastolic filling is nearly sufficient to meet the oxygen demands of the body. Progressive increases in oxygen demand may result in increases in the force of atrial systolic contraction. The combination of a low A_{TDE} at rest and the ability to progressively increase A_{TDE} (and thus reduce their E_{TDE} / A_{TDE} ratio) through exercise may be one mechanism by which endurance trained athletes maintain or increase their stroke volume up to peak exercise as has been reported (Gledhill *et al.,* 1994). Colan *et al.,* (1992) demonstrated augmented systolic mechanics in endurance trained athletes at rest compared to controls and also concluded that the changes were due to a higher functional reserve in athletes. Schmidt - Truckass *et al.,* (2001) also determined E_{TDE} / A_{TDE} sub - endocardial velocities were different between endurance trained athletes and controls. However, their data measured endocardial motion of a composite axis towards the centre of contraction, rather than in either the short or long axis. Unlike Scmidt - Truuckass *et al.,* (2001) A_{TDE} velocities between runners and controls approached ($p = 0.74$) but did not reach significance in this study, and E_{TDE} velocities were significantly different.

While it is probable that the improved diastolic performance of the runners allows high stroke volumes at high heart rates, the mechanism behind the increased E_{TDE} and the altered E_{TDE} / A_{TDE} ratio in the endurance trained athletes is unclear. Scmidt - Truckass *et al.,* (2001) suggested the longer diastolic filling time due to endurance training induced bradycardia results in increased mid diastolic atrial emptying and hence a reduction in the force of the atrial systolic contraction at rest as do Finkelhor *et al.,* (1986) and Granger *et al.,* (1985). Although improved mid diastolic atrial emptying would reduce the force of atrial systole at rest, it is difficult to see how changes in ventricular volume and diastolic filling period would have a direct affect on E_{TDE} especially as it has been shown to be unaffected by changes in preload (Sohn *et al.,* 1997; Aranda *et al.,* 1998; Alam *et al.,* 2000). It is possible that the increased E_{TDE} is due to chronic endurance training mediated changes at the molecular level of the myocyte aimed at reducing the half life of the Ca^{2+} signal following contraction. An increase in myocyte sarcoplasmic reticulum Ca^{2+} ATPase, phospholamban and calsequestrin as well as in cell membrane Ca^{2+} pumps would all lead to a reduction in the time constant of sarcoplasmic Ca^{2+} removal. This would in turn increase long axis lusitropic properties. Although animal studies have demonstrated little (Penparkgul *et al.,* 1977) or no change (Laughlin *et al.,* 1989) in some or all these factors following exercise training these studies used relatively short training schedules, and it may be that chronic endurance training may be required. Furthermore, recent evidence has demonstrated an up regulation of genes encoding sarcoplasmic reticulum Ca^{2+} ATPase (SERCA2) following endurance swim training in rats (Buttrick *et al.,* 1994). Also mild LVH in response to mild induced hypertension has also been demonstrated

to up regulate SERCA2 genes but these are down regulated in severe hypertrophy (Masashi *et al.*, 1996). The authors concluded that the increase in SERCA2 activation in mild hypertrophy mirrored changes in physiological hypertrophy, but as the duration of hypertension was increased and the degree of LVH increased, these adaptive changes could not be maintained. However, there are too few studies considering the effect of exercise and / or physiological hypertrophy on Ca^{2+} signal control for definite conclusions to be drawn.

An alternative mechanism may be that endurance trained athletes have greater diastolic sensitivity to beta - adrenergic stimulation at rest. Diastolic activation is dependent upon beta - adrenergic signals (Walsh *et al.*, 1990; Kaumann *et al.*, 1999). Increased sensitivity following endurance training would result in faster resting relaxation velocities of the myocardium. Whether any such increases in sensitivity would still be evident at peak exercise is unknown.

Since other investigators have documented an age related decline in long axis diastolic function (Ohte *et al.*, 1998, Farias 1999), it is possible that endurance training mediated increases in longitudinal diastolic function will prevent or reduce the extent of decrease due to ageing. It is also unknown whether endurance training can increase long axis diastolic function in subjects with known heart disease. Both these ideas present suitable avenues for further investigation.

In this study, an E / A ratio of less than 1 had poor sensitivity for the differential diagnosis (Table 3.4), possible due to pseudo - normalisation of the E / A ratio that occurs in some patients. Further evidence of this is provided by the fact that estimation of PCWP by the E / E_{TDE} ratio as validated by Sunderswaren *et al.*, (1998) suggests elevated filling pressure of the left ventricle in both pathological groups (Figure 3.3) which is necessary for pseudo - normalisation to occur. This is in agreement with previous work by Farias *et al.*, (1999) and Nagueh *et al.*, (2000) as it demonstrates the ability of tissue Doppler analysis of mitral annular motion to differentiate between truly normal mitral inflow, and pseudo - normal inflow due to increased filling pressure.

3.5.2 Differentiation Between Different Types of Pathological Hypertrophy

Systolic anterior movement of the anterior mitral leaflet, and asymmetrical septal hypertrophy have high sensitivity but low specificity for the diagnosis of HCM (Gilbert *et al.*, 1980). Other more promising results have been reported using the transmural gradient of myocardial integrated backscatter (Naito *et al.*, 1994), or the myocardial velocity gradient (Palka *et al.*, 1997). Both parameters measure differences in structure and function between the sub - epicardial and sub - endocardial layers, and suggests that sub - endocardial dysfunction is present in all forms of pathological LVH but the pattern of dysfunction may be different between HCM and systemic hypertension. This study demonstrated that there was no difference in the

heterogeneity index between patients with HCM and patients with systemic hypertension.

3.5.3 Strength Trained Versus Endurance Trained Athletes

The two morphological forms of athletes heart are: strength trained heart usually considered to be concentric pattern hypertrophy and endurance trained heart, usually considered to eccentric pattern hypertrophy (Morganroth *et al.*, 1975). There were no differences between these groups in terms of posterior or septal wall thickness, EDD or left ventricular mass index. However, the runners had a greater EDD index than weightlifters due to their smaller body surface area. These results agree with a recent meta - analysis that showed only minor structural differences between the two types of athletes heart (Pluim & Zwinderman 2000).

3.6 Conclusion

In conclusion, the resting assessment of systolic and diastolic velocities of the mitral annulus, along the long axis assessed by tissue Doppler echocardiography can be used in the differential diagnosis of pathologically or physiologically hypertrophied left ventricles in young (< 35yrs) subjects.

CHAPTER 4: A COMPARISON OF LONG AXIS FUNCTION AT REST IN OLDER SUBJECTS WITH PATHOLOGICAL OR PHYSIOLOGICAL HYPERTROPHY WITH NORMAL CONTROLS

4.1 ABSTRACT

The cardiac cycle cause longitudinal fibres, located in the sub - endocardium, to oscillate the mitral valve during systole and diastole. Such movements of the mitral annulus are referred to as long axis function. To identify echocardiographic indices of long axis function that may differentiate between pathological and physiological left ventricular LV hypertrophy, 60 subjects with different types of LVH were compared, 15 patients with hypertrophic cardiomyopathy (HCM), 15 patients with systemic hypertension (HT), 15 weightlifters (WL), 15 runners (R) and 15 normal subjects (C). All subjects were aged between 36 - 55 years. Standard echocardiographic procedures were performed including measurement of left ventricular mass (LVM), ejection fraction (EF), and Doppler measurements of blood flow in early diastole (E) and atrial systole (A). In addition using tissue Doppler echocardiography (TDE) systolic, early diastolic (E_{TDE}) and atrial systolic (A_{TDE}) velocities of mitral annulus were measured. TDE assessment of mitral movement was performed at four sites on the annulus, lateral, medial inferior and anterior segments. There were no differences in mean age or global ejection fraction between groups. HCM and HT had lower average long axis systolic and E_{TDE} velocities than either athletes or controls, (Systole 8.2 ± 2.2. 8.6 ± 1.8, 10.2 ± 1.5, 9.6 ± 1.8, 10.5 ± 2.0 for HCM, HT, WL, C and R respectively $p < 0.01$, E_{TDE} 6.5 ± 2.2, 8.4 ± 3.5, 11.3 ± 1.8, 11.1 ± 1.2 12.2 ± 3.5 for HCM, HT, WL, C and R respectively, $p < 0.05$ for both variables for diseased groups versus controls or either athletic groups). The best differentiation of pathological from physiological hypertrophy was provided by a mean E_{TDE} of 9 cm s^{-1} (sensitivity 93 %, specificity 95 %). Thus long axis systolic and early diastolic velocities are decreased in patients with pathological hypertrophy, but preserved in athletes. These simple new echocardiographic measures can differentiate between pathological and physiological hypertrophy.

4.2 INTRODUCTION

Ageing is associated with a time dependant decrease in global cardiac function (Lakatta 2000). The changes seen with aging include decreases in EF, FS and a reversal of the mitral inflow E / A ratio. (Lakatta 2000). In addition it has also been reported that in sedentary subjects there is an age related decline in the long axis function of the left ventricle (Onose *et al,* 1999; Yamada *et al.,* 1999; Alam *et al.,* 2000).

The previous study indicated that assessment of both systolic and early diastolic long axis function can accurately differentiate between hypertrophy of the left ventricle in response to physiological or pathological processes in young subjects. It is currently unknown whether these conclusions apply equally to older subjects. As previously discussed pathological left ventricular (LV) hypertrophy is associated with myocardial fibrosis, particularly in the sub - endocardium (Pick *et al.,* 1989; Pearlman *et al.,* 1982; Huysman *et al.,* 1989). It is possible that the age related decrements in global and regional cardiac function may reduce the effectiveness of long axis velocities in the differentiation of pathological and physiological LVH. This study therefore, was designed to test the hypotheses that an assessment of longitudinal function by tissue Doppler measurements of mitral annular motion could provide an echocardiographic criterion that can differentiate between physiological and pathological LVH in older subjects.

4.3 METHODS

4.3.1 SUBJECTS

15 patients with mild obstructive hypertrophic cardiomyopathy (HCM), 15 patients with LVH secondary to systemic hypertension (HT), 15 competitive club runners, 15 weightlifters and a control group of 15 sedentary subjects. The protocol was approved by the local ethics research committee and each subject gave written informed consent. All subjects were male and aged between 36 and 55 years

The methodology used in this study is identical to that already described in chapter 3 of this thesis (See Chapter 3 , Methods p 78).

4.4 RESULTS

Table 4.1 Subjects characteristics for Study 2.

	AGE (Yrs)	*BSA (m^2)*	*HR (bpm)*	*BPS (mm Hg)*	*BPD (mm Hg)*
HCM	44 ± 6	1.8 ± 0.2	67 ± 8	137 ± 12	80 ± 12
Hypertensive	47 ± 4	1.9 ± 0.2	68 ± 12	157 ± 20*	98 ± 10*
Weightlifters	45 ± 9	2.1 ± 0.2	68 ± 11	132 ± 11	84 ± 9
Controls	50 ± 5.	1.9 ± 0.9	69 ± 13	131 ± 8	84 ± 5
Runner	48± 5	1.8 ± 0.6	61 ± 12	132 ± 11	83 ± 8

BSA = Body surface area, HR = heart rate, BPS = Systolic blood pressure, BPD = Diastolic blood pressure. * Indicates significantly different to all other groups, ($p < 0.05$).

Table 4.2 Standard echocardiographic findings for each group.

	HCM	HT	WL	Control	*Runners*
Aortic Outflow (mm)	34 ± 6	35 ± 5	34 ± 3	36 ± 3	36 ± 3
Left Atrium (mm)	42 ± 7	40 ± 7	42 ± 5	37 ± 4	39 ± 6
Right Ventricle (mm)	22 ± 4[2]	22 ± 4[2]	28 ± 3[2]	21 ± 2	23 ± 4
Septum (mm)	17 ± 2[2134]	14 ± 2[23]	13 ± 3[2]	10 ± 1	12 ± 3[2]
EDD (mm)	45 ± 6	50 ± 7	54 ± 5	50 ± 4	51 ± 7
PW (mm)	14 ± 2[23]	13 ± 1[23]	13 ± 2[23]	9 ± 1	11 ± 2[2]
ESD (mm)	25 ± 7	27 ± 7[1]	31 ± 4	30 ± 4	30 ± 2
(IVS + PW) / EDD	.72±0.13[2143]	.56 ± .09[2]	.46 ± 0.06	.38 ± 0.05	0.5 ± 0.14
Septum / PW	1.3 ± 0.2[21]	1.1 ± 0.2	0.9 ± 0.07	1.04 ± 0.13	1.13± 0.17
EF (%)	65 ± 6	64 ± 7	62 ± 7	66 ± 6	64 ± 7
ESWS (10^3 Dynes cm^{-2})	32 ± 9	41 ± 20	38 ± 3	51 ± 14	53 ± 7
LVMI (g m^{-2})	188 ± 42[2]	175 ± 42[2]	183 ± 51[2]	109 ± 15	156 ± 19[2]
Mitral E Wave (cm s^{-1})	65 ± 12	77 ± 12	84 ± 19	79 ± 14	76 ± 15
Mitral A Wave (cm s^{-1})	65 ± 24	75 ± 17	60 ± 10	58 ± 11	62 ± 17
Mitral E / A	1.0 ± 0.4[3]	1.1 ± 0.3	1.2 ± 0.2	1.1 ± 0.2	1.3 ± 0.3
E Dt (ms)	234 ± 77[213]	206 ± 53	190 ± 34	177 ± 34	199 ± 51
IVRT (ms)	115 ± 24	109 ± 27	81 ± 11	86 ± 16	99 ± 23
FPV (cm s^{-1})	44 ± 15[2]	43 ± 18[2]	59 ± 11	66 ± 19	55 ± 18

[1] Denotes significantly different from Weightlifters, [2] denotes significantly different from controls, [3] denotes significantly different from Runners and [4] denotes significant difference to hypertensives. EDD = end diastolic dimension; PW = posterior wall; ESD = end systolic dimension; EF = ejection fraction; ESWS = end systolic wall stress; LVMI = left ventricular mass index; E Dt = E wave deceleration time; IVRT = isovolumetric relaxation time (in milli - seconds); FPV = flow propagation velocity (in milli - seconds). Values are means ± standard deviations.

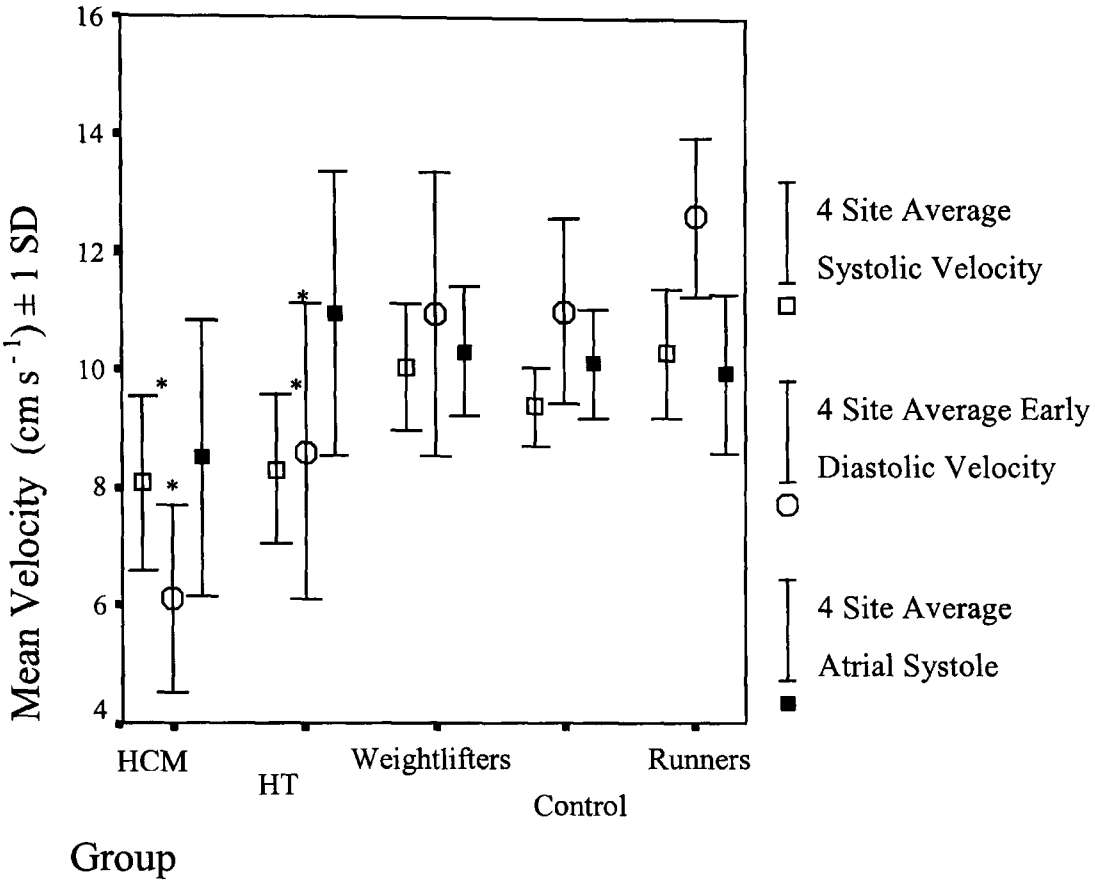

Figure 4.1 Tissue Doppler measurements of the 4 site average for systolic descent and diastolic relaxation velocities. *Denotes significantly different from Controls Weightlifters and Runners

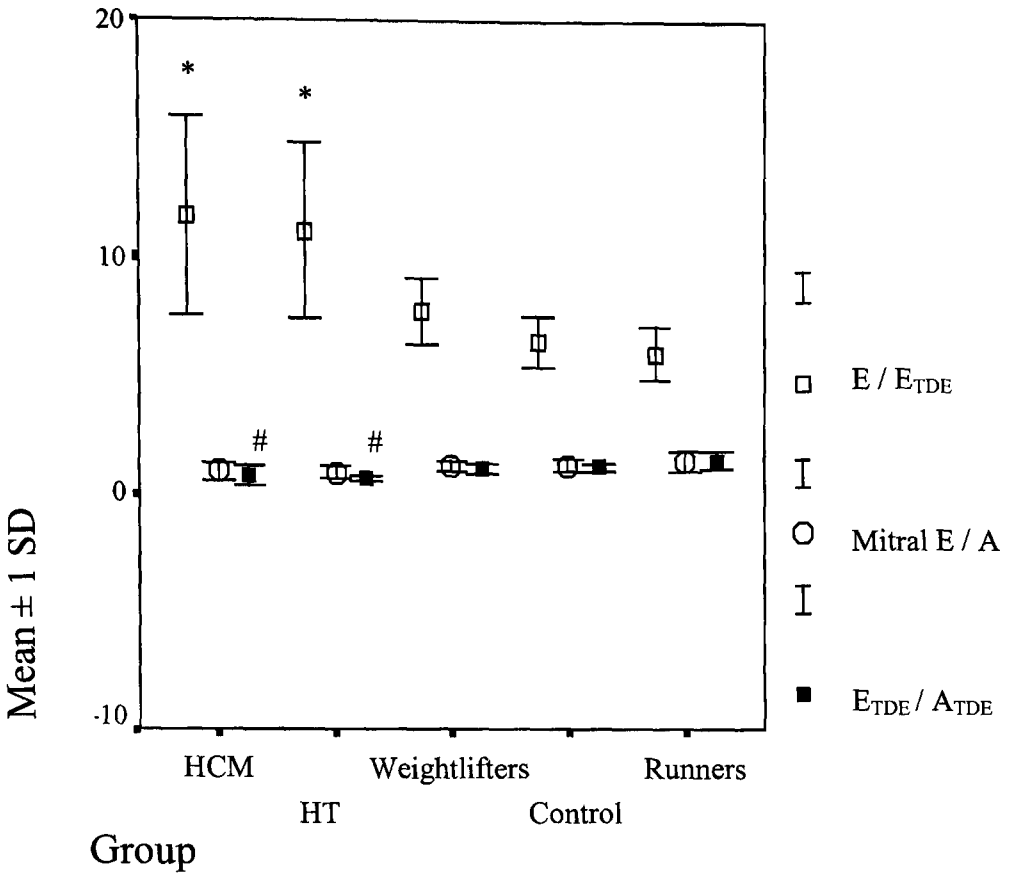

Figure 4.2 E / E_{TDE} , E_{TDE} / A_{TDE} and Mitral inflow E / A ratio's for each group.

* Denotes significantly different from weightlifters, runners and controls, # denotes significantly different from runners only.

Table 4.3 Performance of echocardiographic findings in the discrimination of pathological and physiological hypertrophy.

	Sensitivity	Specificity	Accuracy
4 Site Systolic Descent < 9 cm s^{-1}	87 %	80 %	82 %
4 Site E_{TDE} Velocity < 9 cm s^{-1}	73 %	95 %	90 %
$E_{TDE} / A_{TDE} < 1$	87 %	75 %	50 %
(IVS + LVPW) / LVEDD > 0.6	73 %	95 %	85 %
Mitral E / A ratio < 1	73 %	70 %	71 %
Mitral E / $E_{TDE} < 7$	87 %	65 %	74 %
Flow Propagation Velocity < 50 cm s^{-1}	75 %	80 %	74 %

E_{TDE} = Early diastolic annular velocity, A_{TDE} = Atrial systolic annular velocity, IVS = Inter – ventricular septum, LVPW = left ventricular posterior wall, LVEDD = Left ventricular end diastolic dimension, E = blood flow velocity during early diastole, A = blood flow velocity during atrial systole.

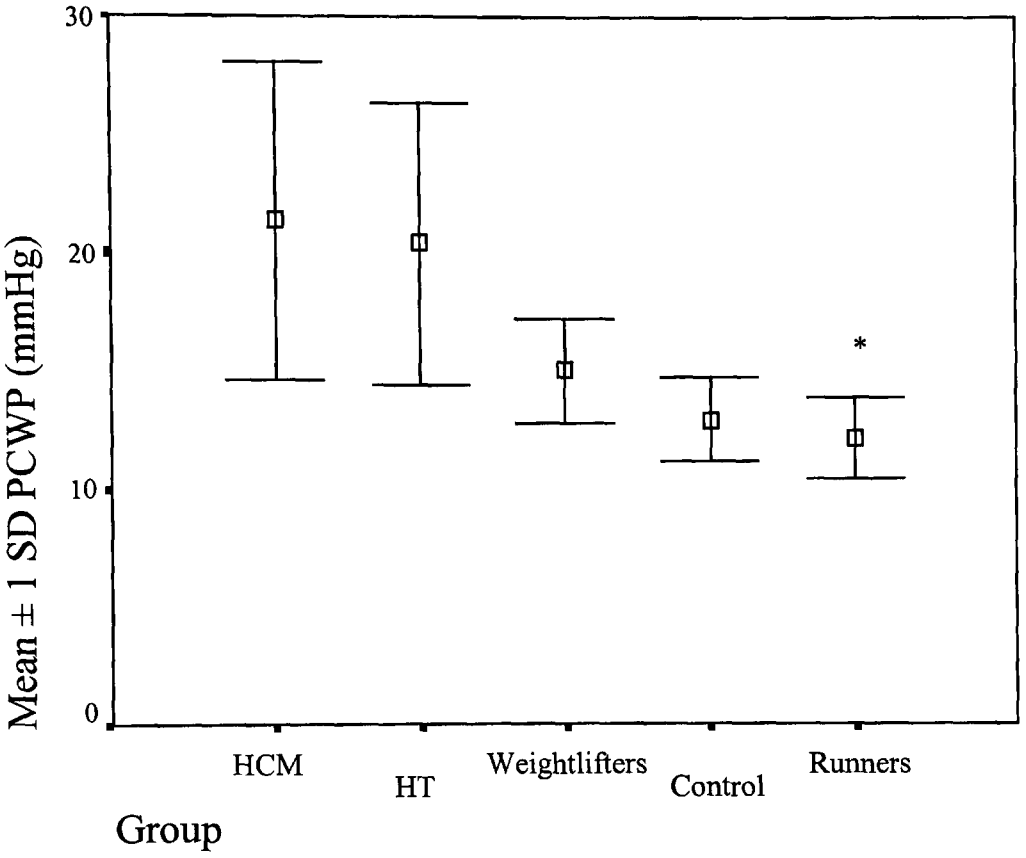

Figure 4.3 Estimated pulmonary capillary wedge pressure (PCWP). From the equation of Sunderswaran *et al* 1998. * Denotes significantly different to HCM and HT

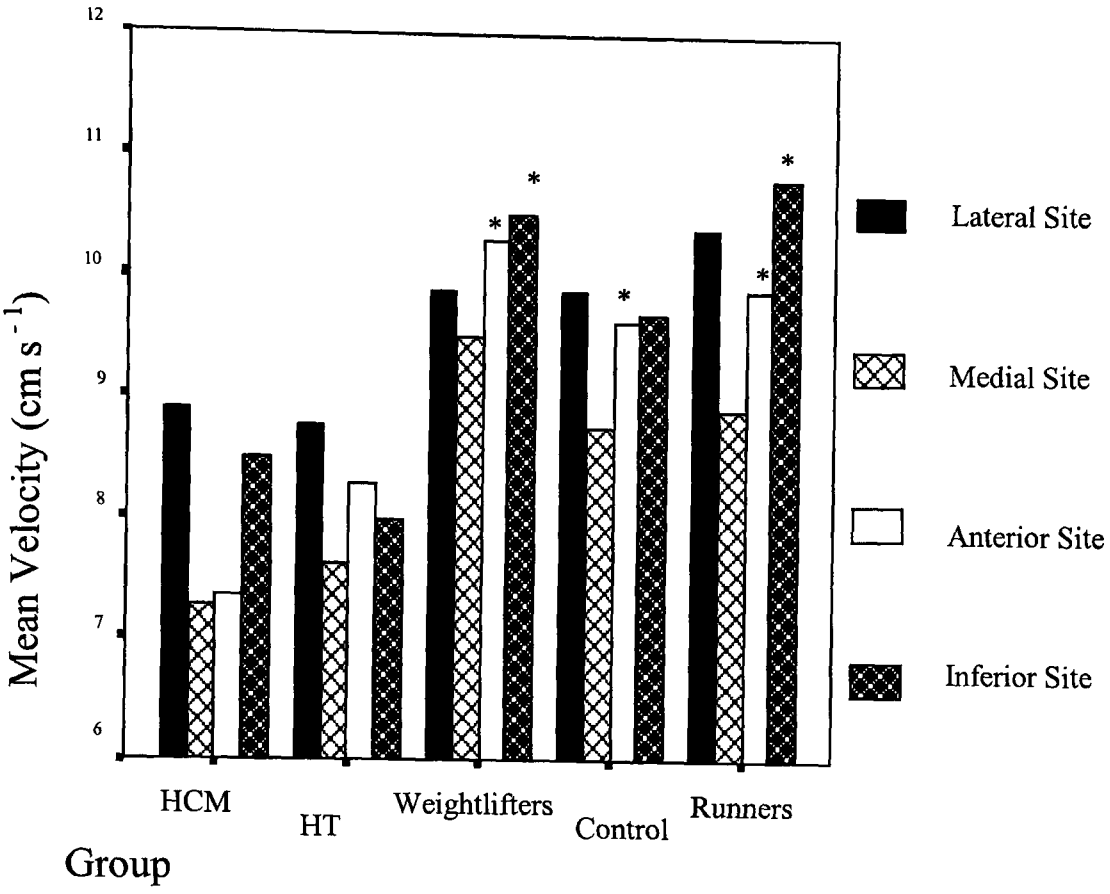

Figure 4.4 Average systolic descent velocity for each of the annular sites for each group. * Denotes significantly different to HCM and HT.

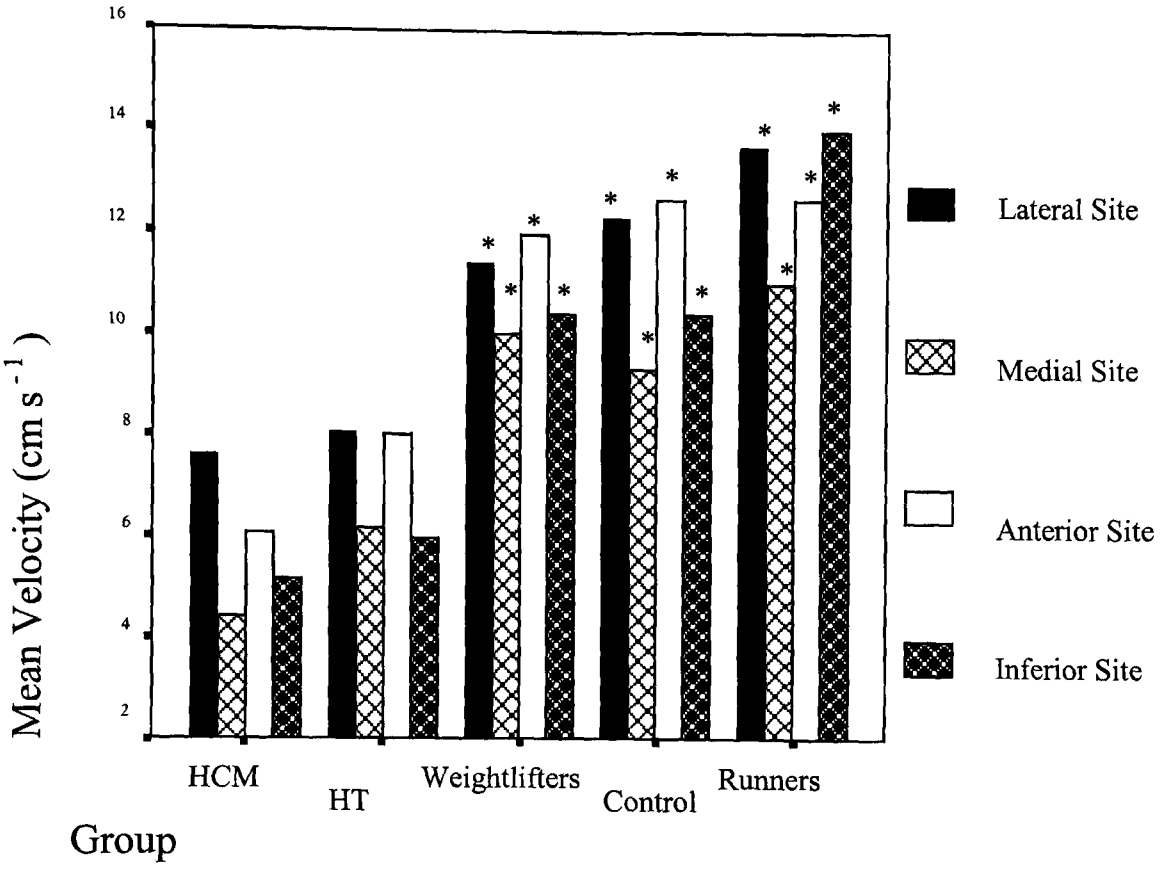

Figure 4.5 Early diastolic relaxation velocities (E_{TDE}) for each of the annular sites. * Denotes significantly different to HCM and HT.

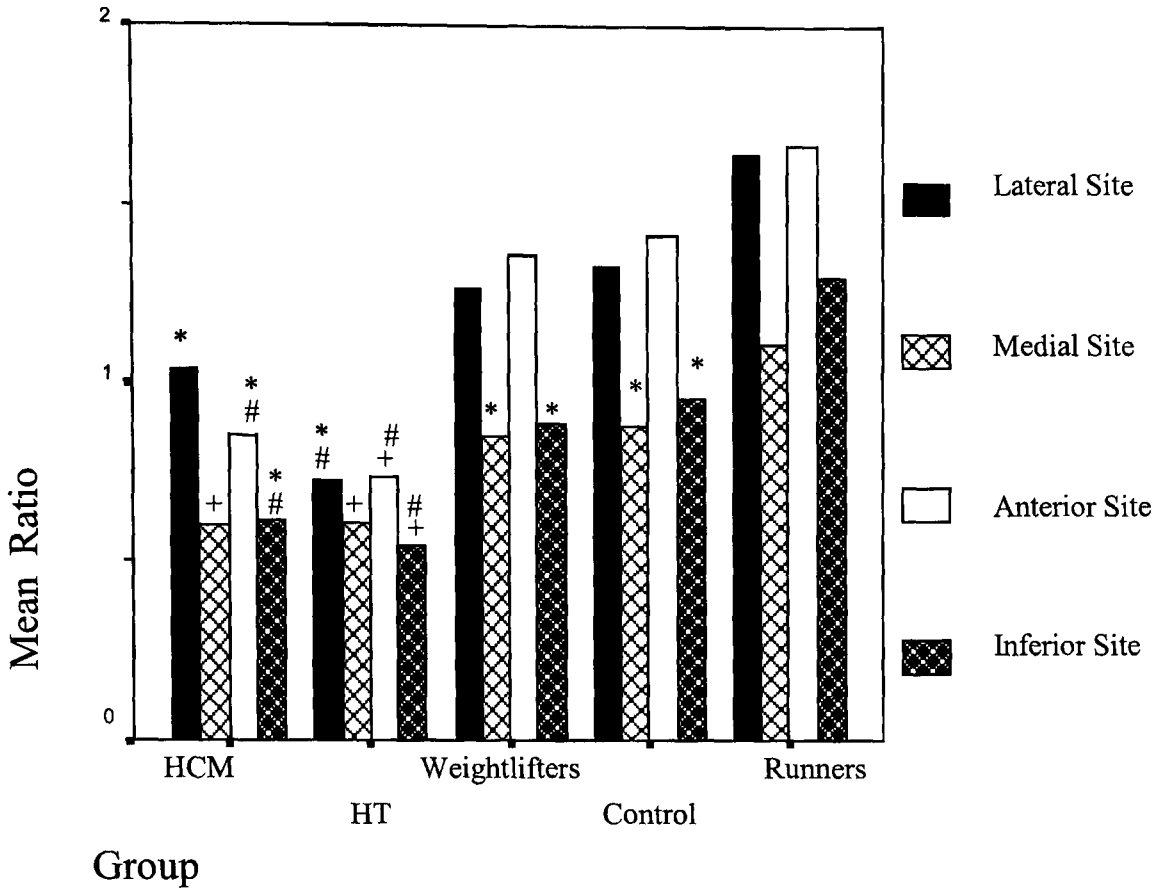

Figure 4.6 E_{TDE} / A_{TDE} ratios at each of the annular sites for each group.

* Denotes $p < 0.05$ compared to runners only; + denotes $p < 0.05$ compared to runners and weightlifters and # denotes $p < 0.05$ compared to controls.

Table 4.4 Tissue Doppler echocardiographic values for velocity of shortening and relaxation along the short axis.

Group	DMIIVS.S	DMIIVS.E	DMIIVS.A	IVS.EA	DMIPW.S	DMIPW.E	DMIPW.A	PW.EA
HCM	5.3 ±1.7	4.3 ± 1.5	5.6 ± 1.7	0.7 ± 0.2	6.9 ± 1.9	7.7 ± 2.4	6.2 ± 2.1	1.4 ± 0.7
HTA	6.1 ±1.2	6.5 ± 1.3	7.2 ± 1.9	0.9 ± 0.3	7.3 ± 1.7	11.8 ± 2.9	5.8 ± 1.5	2.2 ± 1.1
Weightlifters	5.6 ± 1.0	6.7 ± 1.0	6.4 ± 1.6	1.0 ± 0.2	6.9 ± 1.0	16.1 ± 5	5.9 ± 1.3	2.7 ± 0.7
Controls	4.8 ± 1.0	6.4 ± 1.9	5.3 ± 0.8	1.2 ± 0.5	6.7 ± 0.7	14.3 ± 3.5	7.1 ± 2.2	2.2 ± 1.0
Runner	6.8 ± 2.0	6.7 ± 2.8	4.4 ± 1.1	1.4 ± 0.4	6.9 ± 1.4	11.1 ± 3.8	5.9 ± 1.3	2.0 ± 0.8

IVS = inter - ventricular septum, PW = posterior wall, S = systolic velocity, E_{TDE} = early diastolic annular velocity, A_{TDE} = atrial systolic annular velocity, (All values are means in cm s^{-1} except for ratio measures which have no units).

4.4.1 LONG AXIS FUNCTION BY TISSUE DOPPLER

Patients with pathological hypertrophy (both group I and group II) had lower long axis systolic descent velocities than those with physiological hypertrophy at the anterior and inferior sites only. Only the anterior site was significantly different between pathological groups and controls.

Average systolic descent velocity was significantly lower in the HCM and HT groups than in controls, weightlifters or runners as was average early diastolic ascent velocity ($p < 0.01$). Again, there were no differences between groups in the average velocity of A_{TDE}. The high average E_{TDE} and low average A_{TDE} of the runners meant that they displayed significantly greater average E_{TDE} / A_{TDE} ratio than did either the HCM or HT ($p < 0.05$).

Early diastolic velocities of both HCM and HT were lower than those of either athletic groups or controls at all sites of the annulus.(Figure 4.6) late diastolic velocities (A_{TDE}) were not different at any site. Both groups with pathological LVH had significantly lower E_{TDE} / A_{TDE} ratios at all sites of the annulus compared to runners. HT had lower E_{TDE} velocities than weightlifters at all except the lateral site. In addition, runners had significantly greater E_{TDE} velocities than either weightlifters or controls at both the medial and inferior site. ($p < 0.05$ for all differences).

Patients with asymetric septal hypertrophy (ventricular / posterior wall diastolic thickness ratio ≥ 1.3) had lower peak systolic velocities for the medial (6.3 ± 1.1 *v*'s 8.0 ± 0.7 cm s^{-1} $p < 0.05$) and inferior site (6.8 ± 1.1 *v*'s 8.1 ± 0.7, $p < 0.05$) of the mitral sites than patients with concentric hypertrophy. However, diastolic velocities were not different.

Estimated left atrial filling pressure was significantly higher in HCM and HT than in controls or runners but not different to weight trained subjects ($p < 0.05$). In addition 73 % of the pooled pathological LVH subjects displayed apparently normal E / A ratio, while 75 % of those displayed an abnormal E_{TDE} / A_{TDE} ratio and all of them had E_{TDE} below 7 cm s^{-1} and all had estimated PCWP in excess of 19 mm Hg.

4.4.2 ACCURACY FOR DIFFERENTIATING PHYSIOLOGICAL AND PATHOLOGICAL LVH

By analysis of individual sites, the best differentiation between pathological and physiological hypertrophy was provided by a mean systolic anterior annular velocity < 9 cm s^{-1} (Figure 4.1), or by a mean diastolic inferior velocity of 9 cm s^{-1}. From the average of all four sites the best differentiation was from an average systolic descent velocity of 9 cm s^{-1} or a average early diastolic ascent velocity of 9 cm s^{-1}.

From conventional echocardiographic parameters, the best accuracy was found for the ratio of (septum + posterior wall) / EDD. Other traditional echocardiographic

measures were not different between groups (ejection fraction, fractional shortening, E wave deceleration time, flow propagation velocity, isovolumetric relaxation time, $p > 0.05$ between groups for all variables). Using binary logistic regression, testing all variables from Table III the best differentiation was provided by association of mean early diastolic annular velocity < 9 cm s^{-1} , and a mitral inflow E / A ratio < 1 sensitivity 75 %, specificity 100 % and accuracy 86 %, positive predictive power 75 %, negative predictive power 80 %

The sensitivity, specificity and accuracy of the indices of long axis function in comparing physiological hypertrophy with only HCM alone was 87 %, 81 % and 84 % of the average systolic descent velocity. Average diastolic velocity however, was a better discriminator with 100 % 91 % and 95 % for sensitivity specificity and accuracy and had a positive predictive value of 88 % and negative predictive value of 100 %. Septal thickness above 15 mm had a sensitivity of 60 %, a specificity of 90 % and an accuracy of 79 % for the diagnosis of HCM, however septal thickness of 13 mm or above was an inclusion criteria.

4.4.3 Short Axis Function by Tissue Doppler

Short axis systolic and diastolic velocities were not different between the groups, either for ventricular septum or free wall (Table 4.4).

4.4.4 HETEROGENEITY INDEX

Mitral annular systolic velocities were lower in both groups of patients with pathological hypertrophy compared with normal subjects, but they were not different between each other. The heterogeneity index however did discriminate between pathological groups. (1.0 ± 0.46 cm s^{-1} in HCM patients v's 0.52 ± 0.31 cm s^{-1} in patients with hypertension, $p < 0.05$).

4.4.5 INTER ATHLETE COMPARISONS

There were no differences between weightlifters and endurance athletes for age (Table 4.1) or global ejection fraction, (61 ± 5.8 % versus 59 ± 5 %). However, the weightlifters has a greater body surface area (2.1 ± 0.21 versus 1.96 ± 0.17 m^2 $p < 0.01$. There was no difference in septal wall thickness between runners or weightlifters. Despite weightlifters having a thicker posterior wall (13 ± 2 versus 11 ± 2 mm $p < 0.05$), LVM index was not significantly different (183 ± 51 versus 156 ± 19 g m^{-2}). EDD was not different between the two groups however, when corrected for body surface area (EDD index), the runners had a significantly greater EDDi (27.7 ± 1.1 versus 25.0 ± 0.7).

Short axis and long axis velocities were similar between athletes (Table 4.4). Runners did not display better diastolic function, as judged by increased velocities during early diastolic filling. The E / A ratio of mitral inflow was 1.3 ± 0.4 in runners versus 1.2 ± 0.2 in weightlifters $p > 0.05$).

4.5 DISCUSSION

The results of this study indicate that the assessment of longitudinally directed velocities of the mitral annulus measured throughout systole and diastole has the potential to differentiate between pathological and physiological forms of hypertrophy in older subjects. Furthermore, when these measures are allied to other Doppler measurements of haemodynamic inflow, the specificity sensitivity and accuracy of differential diagnosis are increased. The ability of these criteria are improved further when applied only to patients with HCM.

Criteria proposed for distinguishing between pathological and physiological LVH include rest and / or post exercise LV dysfunction, measured by reversal of E / A ratio and / or a prolongation of the E wave deceleration time (Lewis *et al.,* 1992), an increase in LV wall thickness above 16 mm (Pellicia 1991) and an increase in the ratio of septum + posterior wall / end diastolic diameter ratio (Dickuth *et al.,* 1994). Patients with pathological LVH had greater thickness of the ventricular septum than either the weightlifters or the runners; this was an inclusion criteria for the HCM group, thus septal thickness above 15 mm had poor sensitivity but good specificity for the differential diagnosis.

The conventional criteria that differentiated best between pathological and physiological hypertrophy was the ratio of septum + posterior wall / end diastolic diameter, which is in agreement with previous work by Dickuth *et al.,* (1994),

however, this is the first time the efficacy of the criteria set out by Dickuth *et al.*, (1994) has been assessed in older strength and endurance athletes. In this study, the criteria proposed by Dickuth *et al.*, (1994) had reasonable sensitivity specificity and accuracy (73 %, 95 %, 85 % respectively). Furthermore, although these findings were not as good as other methods of differentiation, they are very similar to those documented in the previous study (73 %, 90 %, 82 % respectively) using younger subjects. This indicates that, limitations accepted, the test proposed by Dickuth *et al.*, (1994) is relatively robust in terms of its application to different age stratifications.

In this study the best single predictors of the nature of increased ventricular mass were an average systolic descent velocity < 9 cm s^{-1} and average diastolic velocities of < 9 cm s^{-1} . Binomial logistic regression identified E_{TDE} as the best predictor, and no combination of variables could better predict the cause of increased ventricular mass. This indicates that in older athletes diastolic E_{TDE} velocity is a better predictor than systolic velocity. Combining $E_{TDE} < 9$ with mitral E / A < 1 improved specificity but at the expense of both sensitivity and accuracy (sensitivity 73 % specificity 100 % accuracy 83 %). Furthermore although systolic velocity, individually was a better predictor than mitral E / A ratio, those subjects with reduced E_{TDE} also had a reduced systolic velocity and hence the predictive power of systolic velocity and E_{TDE} together was no better than E_{TDE} alone.

The depressed systolic velocities of both HCM and HT groups along the long axis of the left ventricle, both on average and at the anterior and inferior sites of the annulus

are in agreement with work performed by other investigators (Gulati *et al.*, 1996; Yamada *et al.*, 1999; Tabata *et al.*, 2000). This reduction in systolic velocity is likely due in part to increases in fibrosis of the sub - endocardium which has been demonstrated both in HCM and HT (Pick *et al.*, 1989; Huysman 1989). Fibrosis reduces the number of myocytes available for contraction. As the fibres governing longitudinal motion make up a small proportion of the ventricular walls, the removal of any given number of myocytes will generate a correspondingly greater decrease in performance, than if the same amount were removed from circumferential fibres. Furthermore, the increased fibrosis along with the increases in type III collagen content (thick inelastic fibres) demonstrated in overload hypertrophy (Pick *et al.*, 1989) may also decrease ventricular compliance and thus affect diastolic relaxation velocities. In addition, some degree of sub - clinical ischaemia may also contribute to reduced systolic velocity. Several investigators have demonstrated that the sub - endocardium is the largest contributor to wall thickening during systole. (Myers *et al.*, 1986; Gallagher *et al.*, 1982). Therefore, in basal conditions, there is a greater oxygen demand at the level of the sub - endocardium than in less deep myocardial layers (Collona *et al.*, 1999). In ischaemic conditions, due to this greater oxygen demand, the sub - endocardium is the first vulnerable layer (Collona *et al.*, 1999). Since reduced coronary reserve has been demonstrated in hypertension due to increased arteriolar wall thickness (Gavin *et al.*, 1998) and hypertrophic cardiomyopathy due to the failure of angiogenesis to match myocyte growth (Yarom *et al.*, 1992). Sub - clinical ischaemia, or ischaemia of the sub - endocardium may be responsible for reduced long axis contraction velocities.

The decrease in diastolic velocities may be due to impaired calcium uptake by the sarcoplasmic reticulum in HCM and HT (Mukherjee & Spinale 1998). This would result an increase in the decay period of the Ca^{2+} transient and result in reduced relaxation velocity. Furthermore, this has been demonstrated as a general response to pathological increases in cardiac mass in compensated heart disease (Schotten *et al.*, 1999) and to myocardial ischaemia (Ming *et al.*, 1994). It is therefore possible that the ischaemia outlined earlier and / or a negative lusitropic adaptation to increased mass are responsible for reductions in diastolic contraction velocities in these subjects.

While the reduction in function demonstrated in the HCM and HT groups has been documented previously. There are no previous data on the long axis function in senior athletes. The data demonstrate that chronic physical exercise whether endurance or resistance in nature does not improve resting systolic longitudinal function above that of healthy older controls. While there was a tendency for the runners to display a higher systolic velocity than controls both in terms of average of all sites and at all except the anterior site it did not reach significance, whether this would be the case in senior elite athletes in unknown. In contrast to this, while the controls and both athletic groups demonstrated significantly greater E_{TDE} velocities than the pathological groups. The runners demonstrated a significantly greater E_{TDE} / A_{TDE} ratio at two sites (medial and inferior) compared to both weightlifters and controls. Although these differences became non - significant when expressed as the average of all four sites it is still indicates improved diastolic relaxation profile in senior endurance athletes. Furthermore, the endurance athletes were the only group to have a significantly higher

E_{TDE} / A_{TDE} ratio than either pathological group. This may be indicative of senior endurance athletes ventricles working at a lower level of their functional capacity at rest. This is because the reduced A_{TDE} indicates a reduced force of atrial contraction at rest in endurance athletes. Assuming the maximal A_{TDE} possible for endurance athletes is similar to that of controls or weightlifters, then it is likely that during exercise conditions the A_{TDE} of endurance athletes increases. Increased force of atrial contraction and a progressive reduction of the E_{TDE} / A_{TDE} ratio may be one of the mechanisms that allow endurance trained athletes to maintain or increase stroke volume up to $\dot{V}O_{2MAX}$ as has been described by previous investigators (Gledhill *et al.*, 1994). In addition the high E_{TDE} of the endurance athletes meant they had a lower estimated left atrial filling pressure (PCWP Figure 4.3). This is in agreement with Colan *et al.*, (1987) who described endurance athletes as having reduced preload at rest as the ventricle is adapted for long periods with high cardiac output. This reduced preload at rest is similar to changes seen with venodilators in cardiomyopathy patients (Colan *et al.*, 1987). This may also give the endurance athletes the ability to increase stroke volume during exercise, as they have a greater potential to increase filling pressure and hence rate of ventricular filling which would be necessary to increase stroke volume at high heart rates. This data demonstrates improved diastolic function in older endurance athletes, similar, but of lower magnitude, to the changes documented in the previous study in younger athletes. This suggests that it is possible to maintain normal cardiac function into old age.

Identification of pseudo - normal mitral E / A ratios was possible using long axis tissue Doppler examination. Subjects from either pathological group who exhibited normal mitral E / A ratios all had poor relaxation velocities and all had very high estimated pulmonary capillary wedge pressure (> 19 mm Hg). Although abnormal E_{TDE} / A_{TDE} ratio has been suggested as a method of differentiating normal and pseudonormal mitral E / A profiles, in this study the E / E_{TDE} ratio (or its derivative estimated PCWP) was better at identifying pseudo - normal filling profiles.

4.5.1 Differentiation Between Different Types of Pathological Hypertrophy

Systolic anterior movement of the anterior mitral leaflet, and asymmetrical septal hypertrophy have high sensitivity but low specificity for the diagnosis of HCM (Gilbert *et al.,* 1980). Other more promising results have been reported using the transmural gradient of myocardial integrated backscatter (Naito *et al.,* 1994), or the myocardial velocity gradient (Palka *et al.,* 1997). Both parameters measure differences in structure and function between the sub - epicardial and sub - endocardial layers, and suggests that sub - endocardial dysfunction is present in all forms of pathological LVH but the pattern of dysfunction may be different between HCM and systemic hypertension. This study demonstrated that patients with HCM had low annular velocities and high heterogeneity, suggesting localised or patchy sub endocardial dysfunction whereas patients with systemic hypertension also had low

velocities but little heterogeneity, probably related to diffuse sub endocardial dysfunction.

4.5.2 Strength Trained Versus Endurance Trained Athletes

There were no differences in systolic velocities between these groups, but runners had better diastolic function whether assessed globally or regionally in the long axis. These results fit with a meta - analysis that showed only minor structural differences between the two types of athletes heart (Pluim & Zwinderman 2000).

4.6 Conclusion

The assessment of long axis function in older subjects has the capability of differentiating between those with pathological and those with physiological hypertrophy. Furthermore, endurance training appears to maintain benefits in diastolic function.

CHAPTER 5: AGE RELATED CHANGES IN LONG AXIS FUNCTION: COMPARISONS AND CORRELATIONS FROM STUDIES I AND II

5.1 ABSTRACT

Ageing, athletic training and pathology are all associated with changes in long axis function. However, there is little information of the interaction of these factors and their resultant effect on long axis function. Therefore, the purpose of this study was to use the pooled data from previous studies in order to determine the magnitude of effect any such interactions would have. Using the data from studies 1 and 2, age related changes in the hypertrophic cardiomyopathy (HCM), hypertensives (HT), weight lifter (WL) runner (R) and control (C) groups. Pearson product moment correlations were performed in order to identify age related changes within groups. 2 Way ANOVA was also used to determine significant changes between younger and older subjects of the same cardiac group. Neither WL, R HCM or HT had age related reductions in long axis systolic function ($p > 0.05$), while C age related systolic reductions were significant ($r = - 0.7$, $p < 0.05$). Only C and R demonstrated significant age related reductions in diastolic long axis function, both in terms of E_{TDE} ($r = - 0.6$ and $- 0.7$ for C and R respectively, $p < 0.05$) and A_{TDE} ($r = - 0.5$ and $- 0.6$ for C and R respectively, $p < 0.5$). Despite this age related decline, the diastolic long axis function of older R was above that of younger C ($p < 0.05$ for both A_{TDE} and E_{TDE} for older R versus younger C). Furthermore no groups demonstrated any change age related change in short axis function. Taken together these data indicate that both WL and R demonstrated preservation of long axis function, although in R diastolic values fell from the very high levels seen in younger R, while C demonstrated age related reductions in all parameters of long axis function. Diseased groups had no greater fall in long axis function, possibly indicating no summation of effects of age and disease. Furthermore the functional age related changes appear to be confined to the long axis.

5.2 INTRODUCTION

There is little information to date regarding the effects of ageing on resting longitudinal function. Of the three studies that have examined ageing, all have looked at its effects on normal healthy subjects. (Onose et al., 1999; Alam et al., 1999; Yamada 1999). There is currently no data available on the effects of age concomitant with disease, or with endurance or resistance training. Of particular interest is whether chronic exercise training of either endurance or resistance type, can reduce or prevent the age related decline noted in normal subjects (Onose et al., 1999; Alam et al., 1999; Yamada et al., 1999). It is also unknown whether the age related decline further compounds reductions in function seen in pathological states.

This chapter will examine the age related changes in hypertrophic cardiomyopathy (HCM) hypertensive LVH (HT) controls weightlifters and runners, using pooled data collected in studies I and II.

5.3 METHODS

Subjects were pooled from study 1 and study 2. The data collection was as previously described for study 1 (See Chapter 3, Methods p78).

5.3.1 STATISTICAL ANALYSIS

For the purpose of this comparison the pooled data from studies I and II were used. Age related changes were determined using Pearson product moment correlation (Thomas and Nelson 1996), and were considered significant if $p < 0.05$. Differences between age groups were calculated using a 2 way ANOVA with age (2 levels younger / older) and group (5 levels, HCM, HT, controls, runners weightlifters) specific differences were determined using a post hoc Sheffe test (Thomas and Nelson 1996), with significance being determined at the $p < 0.05$ level. Statistical analysis was performed using SPSS (V. 9.0).

5.4 RESULTS

From the correlations, the runners had no age related decline in the average 4 site systolic descent velocity. E_{TDE} demonstrated an age related decrease while A_{TDE} demonstrated an age related increase. The older runners therefore had lower E_{TDE} / A_{TDE} ratio's. They also demonstrated an age related increase in systolic blood pressure, and reduction in EDD, and hence in the derived EDV. While the mitral E and A did not vary with age there was an age related decrease in mitral E / A ratio. The younger runners demonstrated faster systolic, E_{TDE}, and A_{TDE} velocities as well as higher E_{TDE} / A_{TDE} and E / A ratios.

The weightlifters did not display any age related decreases in any measures of long axis function. They did demonstrate an age related decrease in end systolic wall stress. Furthermore, the older weightlifters were not significantly different to younger weightlifters in any of the TDE assessments.

Controls had strong negative correlations between age and systolic long axis function (averaged over 4 sites), and diastolic E_{TDE}. This was in tandem with a significant age related increase in A_{TDE} and therefore resulted in a significant age related decrease in the E_{TDE} / A_{TDE} ratio. The control group also had a significant age related increase in diastolic blood pressure, as well as in posterior wall thickness. They also demonstrated an age related increase in mitral E wave and decrease in mitral E / A ratio. The younger controls demonstrated a significantly higher E_{TDE}, E_{TDE} / A_{TDE} ratio and mitral E / A ratio.

The pooled HCM group had no significant age related changes in either systolic E_{TDE} or A_{TDE} measures. However, they did show a significant age related decrease in the E_{TDE} / A_{TDE} ratio and demonstrated significant age related increase in mitral A velocity and decrease in the mitral E / A ratio. There were also no significant differences between the older HCM and younger HCM group in any of the TDE assessments.

In the pooled HT group E_{TDE} / A_{TDE} ratio was the only variable to significantly correlate with age. Of the other echo variables the pooled HT group demonstrated significant age related increases in septal thickness and also end diastolic volume. Also mitral A wave and mitral E / A ratio correlated significantly with age. Additionally, there were no significant differences between the older and younger HT groups for any of the TDE variables.

Table 5.1 Differences between different age groups of the same cardiac group.

	Av. Sysc	*Av E_{TDE}*	*Av. A_{TDE}*	*E_{TDE} / A_{TDE}*	*Mitral E /A*
Young HCM v's Older HCM	N / S	N / S	N / S	N / S	N / S
Young HT V's Older HT	N / S	N / S	N / S	N / S	N / S
Young WL V's Older WL	N / S	N / S	N / S	N / S	N / S
Young Con V's Older Con	N / S	*	N / S	*	*
Young Run V's Older Run	*	*	+	*	*

HT = Hypertensives, WL = Weightlifters, Con = Controls, Run = Runners, Syst = Systolic annular velocity, E_{TDE} = Early diastolic annular velocity, A_{TDE} = Atrial systolic annular velocity, E = Blood flow velocity during early diastole, A = Blood flow velocity during atrial systole. * Signifies $p < 0.05$ for younger groups greater than the older group, + signifies $p < 0.05$ for younger group less than older group, and N / S = no significant difference.

Table 5.2 Group correlation coefficients for age and selected variables.

		HCM	*HT*	*Controls*	*Weight Lifters*	*Runner*
4 Site Syst.	Significance	0.109	- 0.039	- 0.696	- 0.289	- 0.359
	Correlation	0.698	0.890	**0.015**	0.297	0.189
4 Site E_{TDE}	Correlation	- 0.411	- 0.338	- 0.586	- 0.441	- 0.672
	Significance	0.128	0.218	**0.007**	0.100	**0.026**
4 Site A_{TDE}	Correlation	0.440	0.273	0.541	0.149	0.579
	Significance	0.101	0.325	**0.041**	0.597	**0.024**
E_{TDE} / A_{TDE}	Correlation	- 0.495	- 0.570	- 0.651	- 0.451	- 0.671
	Significance	**0.041**	**0.026**	**0.002**	0.092	**0.006**
Estimated PCWP	Correlation	0.332	0.359	0.067	0.446	0.286
	Significance	0.227	0.189	0.778	0.096	0.302
EF	Correlation	0.110	- 0.004	- 0.197	- 0.076	- 0.044
	Significance	0.697	0.990	0.419	0.787	0.877
LVMASSi	Correlation	0.011	0.401	0.299	0.096	- 0.105
	Significance	0.970	0.139	0.200	0.734	0.709

HT = Hypertensives, WL = Weightlifters, Con = Controls, Run = Runners. Systolic = Systolic annular velocity, E_{TDE} = Early diastolic annular velocity, A_{TDE} = Atrial systolic annular velocity, E = Blood flow velocity during early diastole, A = Blood flow velocity during atrial systole. PCWP = Pulmonary capillary wedge pressure (estimated from Suderswaren *et al.*, 1998), EF = Ejection fraction, LVMASSi = Left venytricular mass index. Significant correlations are printed in bold.

Table 5.3 Correlations between age and selected variables for each group. Any variable omitted contained no significant correlations.

		HCM	*HT*	*Control*	*Weight Lifter*	*Runners*
BPS	Correlation	0.464	0.090	0.283	- 0.006	0.535
	Significance	0.081	0.750	0.226	0.983	**0.040**
BPD	Correlation	0.027	- 0.113	0.657	0.165	0.396
	Significance	0.924	0.689	**0.002**	0.557	0.144
End DD	Correlation	- 0.203	0.139	0.016	- 0.132	- 0.591
	Significance	0.467	0.622	0.946	0.638	**0.020**
PW	Correlation	0.279	0.160	0.428	0.329	- 0.101
	Significance	0.313	0.569	**0.049**	0.231	0.720
IVS	Correlation	0.049	0.623	0.083	- 0.042	0.417
	Significance	0.862	**0.013**	0.729	0.881	0.122
EDV	Correlation	0.109	0.539	- 0.015	- 0.287	- 0.573
	Significance	0.698	**0.038**	0.952	0.300	**0.025**
ESWS	Correlation	- 0.310	0.000	- 0.266	- 0.583	- 0.158
	Significance	0.302	0.999	0.257	**0.023**	0.574
MITRAL E	Correlation	0.081	- 0.111	- 0.475	0.179	- 0.277
	Significance	0.775	0.695	**0.034**	0.524	0.317
MITRAL A	Correlation	0.687	0.647	0.143	0.348	0.437
	Significance	**0.005**	**0.009**	0.549	0.203	0.103
MITRAL E / A	Correlation	- 0.594	- 0.520	- 0.608	- 0.349	- 0.628
	Significance	**0.020**	**0.047**	**0.004**	0.203	**0.012**

BPS = Systolic blood pressure, BPD = Diastolic blood pressure, End DD = End diastolic dimension of the left ventricle, PW = Thickness of the posterior wall at end diastole, IVS = Inter – ventricular septum thickness at end diastole, EDV = End diastolic volume, ESWS = End systolic wall stress, , Mitral E = Blood flow velocity during early diastolic filling, Mitral A = Blood flow velocity during early diastolic filling.

5.5 DISCUSSION

5.5.1 GROUPS WITH PATHOLOGICAL LVH

There are no previous data available on the effect of aging on long axis function in either HCM or HT patients. Neither of the groups with pathological LVH had any significant age - related decrements in longitudinal function. Before firm conclusions can be made a few points should be considered. The effects, of both HCM and HT are not pre - determined for all subjects. The severity of either disease can be affected by the rate of onset, duration and underlying cause of the disease (Julian & Cowan 1992). Furthermore, there is wide variation in the response and prognosis of individuals. Some may decline to heart failure while others may stay in compensated heart failure, despite severe LVH for some years (Julian & Cowan 1992). Thus the assumption that older subjects are in a more advanced stage of heart disease is not necessarily valid. Indeed given these points, and the lack of appreciable differences between younger or older patients in either disease group for ejection fraction or fractional shortening it is likely that both young and old groups were in similar stages of heart disease. With this in mind certain conclusions may be made from the data.

There was no significant correlation between age and systolic or diastolic long axis velocities. This would suggest that the effect of pathology alone is responsible for the long axis velocities of both HCM and HT rather than a summation of both age related reduction and pathology. There was however a significant age related decrease in the

E_{TDE} / A_{TDE} ratio in both HCM and HT. Furthermore, this was of a similar significance to that seen in controls and was concomitant with decreases in mitral E / A ratio. It is reasonable to assume that aging in pathological conditions is associated with the same age related increase in reliance on atrial systolic filling at rest. While the cause of this age related decrease in E_{TDE} / A_{TDE} and E / A cannot be definitively explained, if the previous statement that all subjects in the pooled HCM and the pooled HT groups were at similar levels of disease progression, then it would seem likely that the decrease is due to the underlying effects of age on diastolic filling, i.e. early diastolic dysfunction resulting in greater reliance on atrial systole.

The comparison of different aged groups of subjects with either HCM or HT demonstrates that any age related reduction in systolic or E_{TDE} function occurs secondary to reductions due to pathological processes. The pathological reduction in function, being the greatest is the only apparent measurable change in long axis function. Furthermore, it is not possible to estimate the effect of disease progression of longitudinal function from this data. However, the age related reduction in diastolic function seen in normal subjects along the long axis appears to occur equally in subjects with HCM or HT.

5.5.2 Groups with Physiological LVH and Controls

The control subjects demonstrated a significant age related reduction in all of the measures of longitudinal function (systolic, E_{TDE} and A_{TDE} velocities and E_{TDE} / A_{TDE} ratio). The findings of the control group are not unique, with significant negative

correlations between age and systolic descent velocity (Onose et al., 1999; Alam et al., 1999) E_{TDE} (Alam et al., 1999) and E_{TDE} / A_{TDE} ratio (Alam et al., 1999; Yamada et al., 1999) and positive correlations between age and A_{TDE} (Yamada 1999) have all been documented before. The reason for the altered resting function with age is unclear. The decreased diastolic dynamics has been ascribed to reductions in chamber compliance (Lakatta 2000). The data here would broadly agree with this hypothesis. Reduced compliance would necessitate an increase in atrial filling which would require a greater atrial systolic function at rest. Both these findings are evident in the control group of this study, there is an age dependent increase in both the mitral A wave and in the A_{TDE} velocity, both of which are indicative of increased atrial contribution to diastolic filling and may be evidence of mild restrictive filling. However, other mechanisms have also been suggested. Sub - clinical sub - endocardial ischaemia may increase the decay time for the intracellular Ca^{2+} due to reduced clearance rates by the myocyte sarcoplasmic reticulum, causing an increase in myocyte relaxation time. This is also supported by the data here due to the age dependant increase in long axis relaxation rate. The reduction in both systolic contraction velocity and diastolic relaxation velocity with age may be due to increased fibrosis, decreased sensitivity to beta - adrenergic stimulation which would affect both systolic and diastolic relaxation velocities (Walsh *et al.,* 1990) and reduced activation of L - type calcium channels (Mukherjee & Spinale 1998). The activity of the sympathetic nervous system seems to increase with age, as suggested by higher blood levels of norepinephrine and epinephrine in older than in younger persons during any effort (Lakatta *et al.,* 2000). Because levels of norepinephrine and epinephrine are higher, more beta - adrenergic

receptors on cardiac and vascular cell surfaces are occupied. The result is a desensitization of beta - adrenergic receptors, thereby causing a down - regulation of associated intracellular signaling pathways (Lakatta *et al.,* 2000). Such desensitization may account for all or a substantial portion of the age - associated postsynaptic reduction in responsiveness to beta - adrenergic stimulation.

In contrast to this, both athletic groups demonstrated maintenance of systolic annular velocities with no significant negative correlation between age and systolic descent velocity and with no significant difference between the older or younger groups ($p > 0.05$). In addition the weightlifters demonstrated maintained E_{TDE} with respect to age, while the runners demonstrated a significant age related decline in E_{TDE} and increase in A_{TDE} (and thus an age related decrease in E_{TDE} / A_{TDE} ratio). However, while it is obvious that the weightlifters maintained their E_{TDE} velocity with respect to age, the conclusion that the runners did not should be made with caution. The younger runners demonstrated significantly higher, systolic E_{TDE} and lower A_{TDE} velocities than their older counterparts. The age related decline in these variables may be due to an inability to maintain such high performance characteristics with increasing age. Furthermore, the older runners demonstrated no significant difference to any of the healthy younger groups, thus in this respect the older runners did maintain their diastolic long axis function at levels of healthy young controls (although they did not maintain the very high levels seen in younger runners). In addition, although the duration and distances of training for the younger and older runners were not different,

these were self - reported. The possibility of different training intensities between the younger and older runners cannot be discounted.

The mechanism for maintained systolic and diastolic function in athletic groups may be due to exercise - induced preservation of beta - adrenergic response, or maintenance of faster myosin isoenzymes. In addition, improved Ca^{2+} clearance from the myocyte sarcoplasm compared to older controls is one likely method for improved relaxation rates in these subjects. It is of interest that the weightlifters also maintained their long axis function. This indicates that chronic exercise training 'per se' rather than mode of training (endurance / resistance) is the important factor in maintenance of longitudinal function. Studies have documented increases in global systolic pump function (Eshani *et al.,* 1991; Stratton *et al.,* 1994) and diastolic relaxation profiles (Foreman *et al.,* 1992; Spina *et al.,* 1996) in older adults in response to endurance training. This is the first time that exercise has been shown to prevent age related decline in cardiac muscle fiber contraction and relaxation velocities along the long axis.

5.5.3 SHORT AXIS FUNCTION

None of the groups studied demonstrated any significant short axis changes with respect to age. TDE assessment of the septal and posterior wall systolic and diastolic E_{TDE} and A_{TDE} velocities along the short axis showed no correlation with age at all. Furthermore a 2 way ANOVA demonstrated no significant differences within or

between groups for any of the TDE short axis variables i.e. there was no age related decline in short axis function.

This suggests that age related reductions in global pump function, at least at rest are confined to the long axis and thus the fibers of the sub - endocardium. Since there was also an age related decline in mitral E and E / A ratio, it seems likely that the age related changes in left ventricular filling profile may be due to reductions of function in the long axis. This raises the hypothesis that the age related increase in atrial systolic reliance (both A_{TDE} and mitral A wave) are signaled by reductions in early diastolic dynamics of the long axis alone. In other words in basal conditions the mechanism that determines the force of the atrial systole may be the amount of early diastolic lengthening along the long axis. The lesser the long axis lengthening the 'lower' the mitral ring and thus the greater the atrial volume at the end of E_{TDE} and thus a greater Frank - Starling effect may follow. If this is the case then it suggests that only long axis dynamics are involved in signaling atrial contraction (as atrial filling is constant at a given basal state). Furthermore, it follows that maintenance of longitudinal function is the primary site for prevention of age related decreases in cardiac function.

5.6 CONCLUSIONS

Exercise training appears to prevent the age related decline in systolic function. Resistance and endurance training result in diastolic levels similar to those seen in younger controls, although endurance trained athletes may experience a decrease from

very high levels seen in youth. Furthermore, the decrease in cardiac function associated with ageing appears to be confined to the long axis and this may be the direct signaling mechanism that controls atrial contraction.

CHAPTER 6: LONG AXIS FUNCTION PRE AND POST EXERCISE IN ATHLETES WITH PHYSIOLOGICAL HYPERTROPHY AND CONTROLS

6.1 ABSTRACT

To determine left ventricular global and regional function in endurance - trained and strength - trained athletes 15 endurance - trained and 15 strength - trained athletes with left ventricular hypertrophy (172 ± 27 and 188 ± 39 g m^{-2} respectively) were studied. and compared them with 15 sedentary controls. Ejection fraction, diastolic function, and regional longitudinal myocardial velocities (tissue Doppler echocardiography (TDE)), were measured at rest and immediately after exercise. Endurance - trained compared with strength - trained athletes, had lower resting HR (58 ± 10 and 78 ± 6 beats min^{-1} respectively; $p < 0.001$), the increase at peak exercise was greater (+ 224 % and + 132 %; $p < 0.001$). In addition, duration, workload, maximal oxygen consumption and global systolic functional were higher in the endurance athletes. Resting global diastolic function (E / A ratio 1.62 ± 0.40 compared with 1.18 ± 0.23; $p < 0.01$) and long - axis diastolic velocities (E_{TDE} / A_{TDE} ratio 2.2 ± 1.2 in runners compared with 1.09 ± 0.3; $p < 0.01$) were augmented. Systolic velocities were similar. Exercise capacity was best predicted from end - diastolic diameter index and E / A ratio at rest, and end - diastolic volume index and diastolic longitudinal velocity during exercise ($r = 0.74$, $p < 0.001$). In conclusion, endurance - trained athletes had higher left ventricular long - axis diastolic velocities, augmented global early diastolic filling, and greater chronotropic and global systolic functional reserve. Maximal oxygen consumption was determined by diastolic loading and early relaxation rather than by systolic function, suggesting that dynamic exercise improves cardiac performance by an effect on diastolic filling.

6.2 INTRODUCTION

Morganroth *et al.*, (1975) were the first to suggest that two separate forms of athletes' heart can be distinguished. Adaptations to strength training can be accounted for by the blood pressure response during weight lifting, which can increase levels to as high as 320 / 250 mm Hg (MacDougall *et al.*, 1985). Strength trained athletes usually develop large increases in left ventricular wall thickness but only slight increases in left ventricular diameter (Pluim & Zwinderman 2000; Spirito *et al.*, 1994), Although recent evidence suggests these changes may be relative to changes in body size (George *et al.*, 1998). In contrast during endurance - based exercise the heart adapts to both volume and pressure overloads, and endurance trained athletes develop an increase in both left ventricular diameter, and wall thickness through the law of La Place. (Pluim & Zwinderman 2000).

Although cardiac structure and global function have been investigated extensively, mainly at rest there are few data regarding regional function at rest and peak exercise in the two groups of athletes. The ultrasonic technique of Doppler myocardial imaging or tissue Doppler echocardiography (TDE) now facilitates the quantification of myocardial velocities from different ventricular segments. Tissue Doppler data can be acquired in digital format from every region of the ventricles at the same time that gray scale images are acquired; the data can then be analyzed off line (Pasquet 1999). This allows for rapid data acquisition and a more detailed study of regional function following exercise.

Functionally there are two major myocardial layers of the left ventricle. Fibers in the sub - epicardial layer are orientated in a circumferential direction and are responsible for the short axis changes. Those of the sub - endocardial layer are aligned longitudinally between apex and base and determine long axis dynamics (Greenbaum *et al.*, 1981). Longitudinal fibers are anatomically connected to the mitral annulus, their contraction results in systolic displacement of the annulus towards the apex (Jones *et al.*, 1990). In diastole the myocardial E_{TDE} and A_{TDE} velocities quantify the myocardial motion in the phases of passive filling and atrial contraction, respectively. In comparison, short axis or transverse function is measured from parasternal M - mode traces or from TDE sampling of the posterior or septal wall. The previous studies have demonstrated that endurance trained athletes have augmented resting diastolic long axis function, with very fast early relaxation velocities and slower atrial systolic lengthening along the long axis. Such diastolic augmentation may be one way that endurance trained athletes increase their stroke volume through to peak exercise (Gledhill *et al.*, 1994).

The aims of this study were to assess the long axis function of the left ventricle in strength trained and endurance trained athletes at rest and at peak exercise in order to determine any differences in the regional myocardial function that may lead to functional improvements at peak exercise or cardiac reserve in either of the two groups. An additional aim was to identify which aspects of myocardial function correlate best with peak exercise capacity by comparing both athletic groups with control subjects.

6.3 METHODS

6.3.1 SUBJECTS

Fifty male subjects were enrolled into the study: 34 competitive club athletes recruited from sporting clubs (16 weightlifters and 18 long distance runners), and a control group of 16 age matched sedentary normal subjects. Athletes were included if they had increased left ventricular mass index, > 131 g m^{-2} (Devereaux *et al.,* 1987). Each participant had trained for at least 7 hours per week (aerobic or resistance exercise). Three of the weightlifters admitted using anabolic steroids for periods of 2 to 12 months during their training. Both the athletic groups and controls were normotensive non - smokers. All subjects were assessed following abstention from caffeine for ≥ 12 hrs. The local research ethics committee approved the protocol and subjects gave their written informed consent.

6.3.2 BASELINE ECHOCARDIOGRAPHY

Baseline echocardiographic procedure is described previously in chapter 3 (See Chapter 3 Methods p 78), additional measures regarding exercise and post exercise analysis are outlined below.

6.3.3 EXERCISE PROTOCOL

Graded treadmill exercise testing was performed using an extended Bruce protocol, until exhaustion. Blood pressure was assessed a rest and in the final 30 seconds of each stage of the exercise test, using a manual mercury sphygmomanometer. Heart rate was assessed at rest and during the exercise test using a 12 lead electrocardiogram (Marquette Electronics Inc). Ventilatory response including oxygen uptake ($\dot{V}O_2$) were measured throughout the exercise test using an automated on line analyser (MedGraphics Inc Cardiorespiratory Diagnostics System) which was re - calibrated prior to each test. Immediately after the exercise, subjects were placed in the left lateral decubitus position. Tissue Doppler loops from apical views of the parasternal long axis were acquired digitally and then stored, within two minutes of termination of the exercise, for the subsequent measurement of immediate post exercise ejection fractions and post - exercise myocardial velocities; calculations of cardiac output were made from measurements from apical images recorded 30 - 60 seconds after maximal exercise.

6.3.4 STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS software (V 9.0). Results are presented as mean value ± standard deviations. Differences between groups were tested for significance using 2 way mixed design Analysis of Variance (ANOVA), with a Bonferroni correction factor. Post hoc analysis was by Scheffe F test, (Thomas & Nelson 1996). Correlations between variables were performed using the Pearson

product moment correlation. Univariate linear regression analysis was performed and multiple linear regression analysis to identify the best predictors of $\dot{V}O_{2PEAK}$. A $p < 0.05$ for a two tailed test was considered significant.

6.4 RESULTS

General clinical and resting echocardiographic characteristics of the three groups are given in Table 6.1. There were no differences between weightlifters and runners for the duration of training (10 ± 2 hrs / wk for 9 ± 3 years versus 11 ± 2 hrs / wk for 10 ± 5years). Resting heart rate was significantly lower in endurance trained athletes, than in strength trained athletes, (58 ± 10 beats min^{-1} versus 78 ± 6 beats min^{-1}, $p < 0.001$). There was also no difference in the age of each group, 32 ± 3, 29 ± 6 and 31 ± 4 for runners weightlifters and controls respectively $p > 0.05$)

The increase of heart rate from rest to peak exercise was greater in the endurance trained athletes being 132 ± 13 beats (224 %) compared with 103 ± 16 (132 %) in the strength trained athletes ($p < 0.001$), and 110 ± 13 in controls (140 %). However, peak exercise heart rate was not different between the groups. Peak exercise BP was also similar in all three groups (229 ± 15 in runners *v* 223 ± 16 in weightlifters *v* 221 ± 18 mm Hg in normals). Both exercise duration and maximal oxygen consumption were significantly greater in the endurance trained athletes, being 16 ± 2min, and 51 ± 6 ml Kg^{-1} min^{-1} respectively compared with 11.4 ± 2.5 min and 35 ± 7 ml Kg^{-1} min^{-1} in strength trained athletes (all $p < 0.01$). The normal subjects had 13 ± 2 min and 32 ± 7 ml Kg^{-1} min^{-1} (all $p < 0.01$ versus endurance trained athletes).

Table 6.1 General characteristics of each group at rest.

	Weightlifters	*Runners*	*Controls*
Age (yrs)	28 ± 4	29 ± 7	30 ± 5
Body Surface Area (m^2)	2.06 ± 0.19*#	1.89 ± 0.15	199 ± 0.11
Systolic BP (mm Hg)	139 ±12	140 ± 19	136 ± 11
Diastolic BP (mm Hg)	83 ±9	89 ± 9	80 ± 9
Aortic Root (mm)	34 ± 2	33 ± 4	35 ± 3
Left Atrial (mm)	41 ± 5	40 ± 4	37 ± 4
EDD RV (mm)	28 ± 4#	26 ± 3#	21 ± 3
IVS (mm)	13 ±1#	13 ± 1#	10 ± 1
PW (mm)	13 ±1*#	12 ±1#	9 ± 1
EDD LV (mm)	27 ± 3	30 ± 3#	26 ± 1
ESD LV (mm)	17 ± 3	18 ± 2#	15 ± 2
LVMi ($g\ m^{-2}$)	188 ± 39#	172 ± 2#	106 ± 14
Cardiac Index ($L\ min^{-1}\ m^{-2}$)	6.0 ± 1.4*	4.2 ± 1.6	5.1 ± 1.2

BP = blood pressure, Diam = diameter, RV = Right Ventricle, IVS = inter ventricular septum, PW = posterior wall, EDD = end diastolic dimension, ESD = end systolic dimension, LV = Left ventricle, LVMi = left ventricular mass index. # Denotes significantly different from runners, and * denotes significantly different to controls. .

Table 6.2 Exercise variables between groups.

	HR – E (BPM)	*HR - E (BPM)*	*$\dot{V}O_{2PEAK}$ (ml Kg^{-1} min^{-1})*	*Duration (min)*
Weightlifters	78 ± 6*	184 ± 8	34.8 ± 4.3*	11.5 ± 2.6*
Control	79 ± 12*	189 ± 13	33.9 ± 7.8*	13.8 ± 2.1*
Runners	58 ± 10	190 ± 10	51.1 ± 9.8	16.2 ± 2.1

HR = Heart rate, B = Baseline, E = post exercise * denotes significantly different to runners ($p < 0.05$)

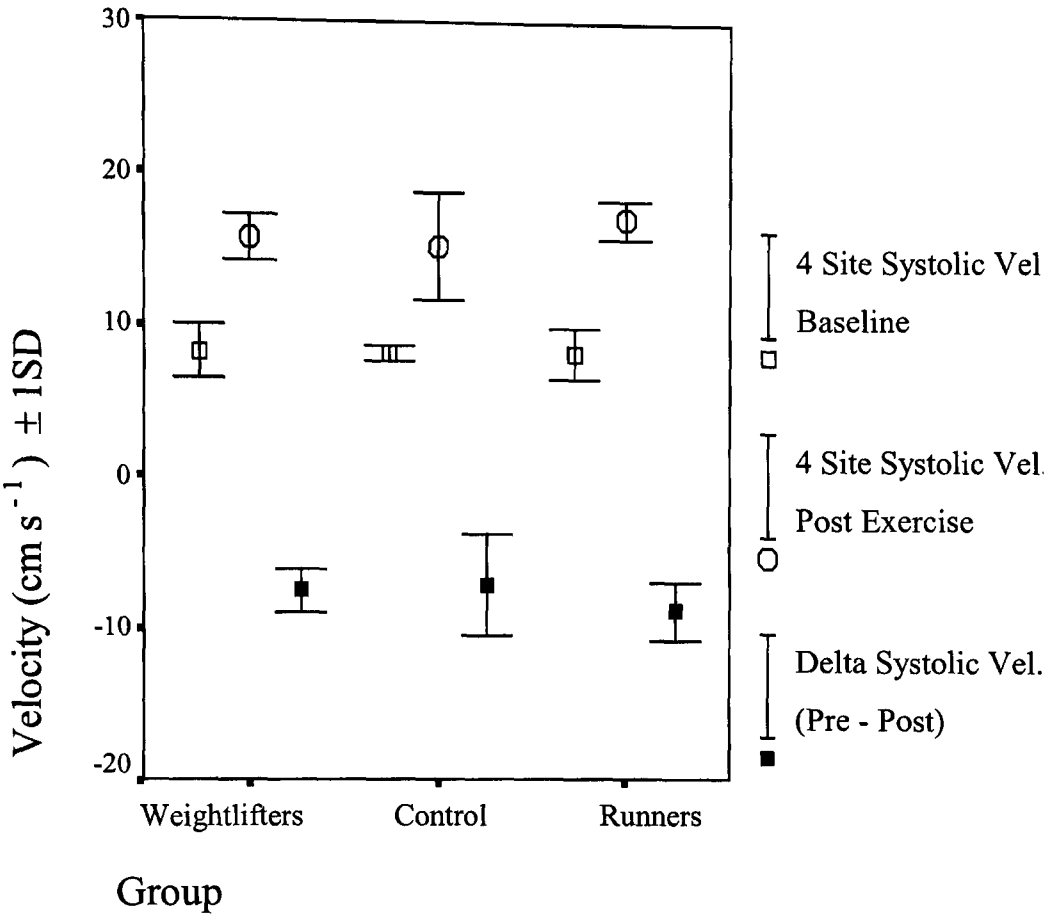

Figure 6.1 Systolic descent velocity along the long axis. Values are averaged across all four sites at baseline, post exercise and the mean change between baseline and exercise.

6.4.1 GLOBAL SYSTOLIC FUNCTION

There were no differences between the groups in resting ejection fraction, (61 ± 5 % versus, 62 ± 6 % versus 66 ± 6 % respectively for runners, weightlifters and normal subjects). On exercise, ejection fraction increased by 18 % from resting values in runners ($p < 0.05$ from rest to exercise), by 12 % in weightlifters ($p < 0.05$) and by 8 % in normals ($p < 0.05$, for runners versus normals $p < 0.05$). However, ejection fraction on exercise did not differ between groups. In both groups of athletes end diastolic volume index did not change from rest to peak exercise (2.6 ± 12 % in runners and 0.5 ± 20 % in weightlifters). Whereas end systolic volume index decreased by – 22 % in runners and by - 18 % in weightlifters ($p < 0.05$). In normal subjects both volume indices decreased at peak exercise (end - diastolic volume – 12 %, end systolic volume – 27 % $p < 0.01$ for both variables). Cardiac index increased by 274 % (from 4.1 ± 1.4 to 13.9 ± 2.2 L min^{-1} m^{-2}) in runners and by 165 % in weightlifters (5.5 ± 1.4 to 14.2 ± 3.5 L min^{-1} m^{-2}) in weightlifters, ($p < 0.001$ for relative increases between runners and weightlifters, peak values n.s.). In comparison, the normal subjects cardiac index rose 142 % from (4.5 ± 1.3 to 10.4 ± 1.9 L min^{-1} m^{-2}).

6.4.2 REGIONAL SYSTOLIC FUNCTION

Resting or peak exercise systolic velocities were not different between the three groups, for either left ventricular long axis contraction (Figure 6.1) or short axis contraction, (Table 6.4). Long axis systolic velocity averaged at the four sites

increased at peak exercise by 114 ± 37 % in runners, 110 ± 44 % in weightlifters, and by 101 ± 42 % in normal subject. In the short axis systolic velocities in the posterior wall increased by 133 ± 71 % in runners, 148 ± 76 % in weightlifters, and 94 ± 56 % in normal ($p < 0.05$ for weightlifters versus controls). In the IVS systolic velocities increased 110 % ± 70 for runners, 170 ± 193 % in weightlifters and 118 ± 104 % in controls (p = ns for all comparisons)

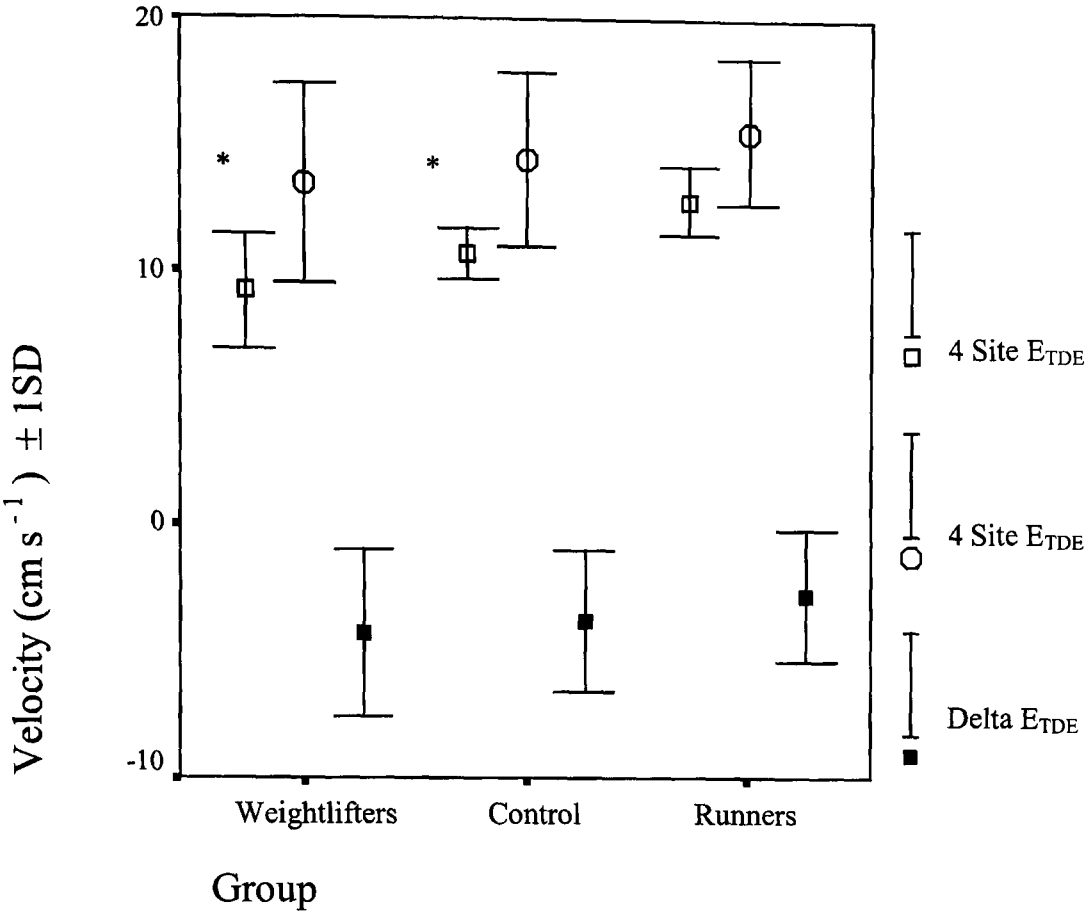

Figure 6.2 Early diastolic relaxation velocities (E_{TDE}) averaged across all four sites. * Denotes significantly different to runners.

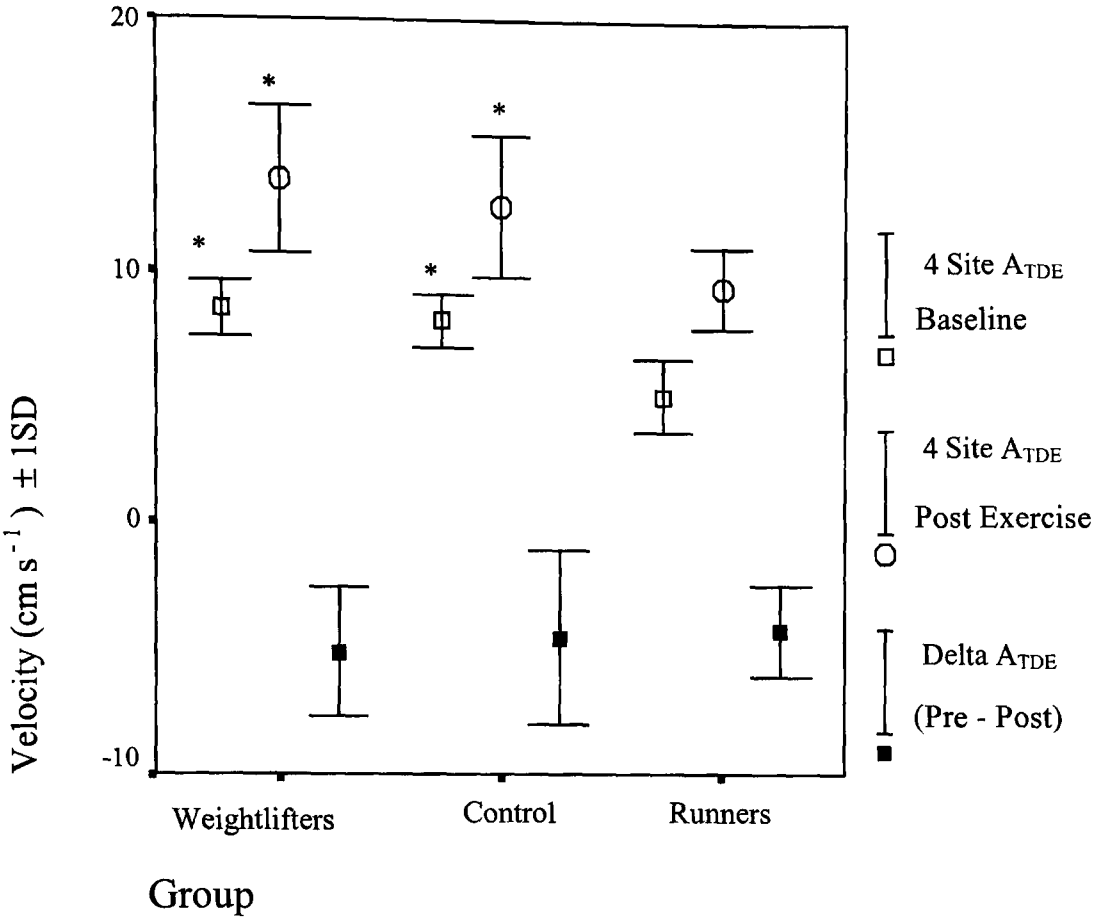

Figure 6.3 Long axis velocities during atrial systole (A_{TDE}). Values are averages of all four sites. * denotes significantly different to runners

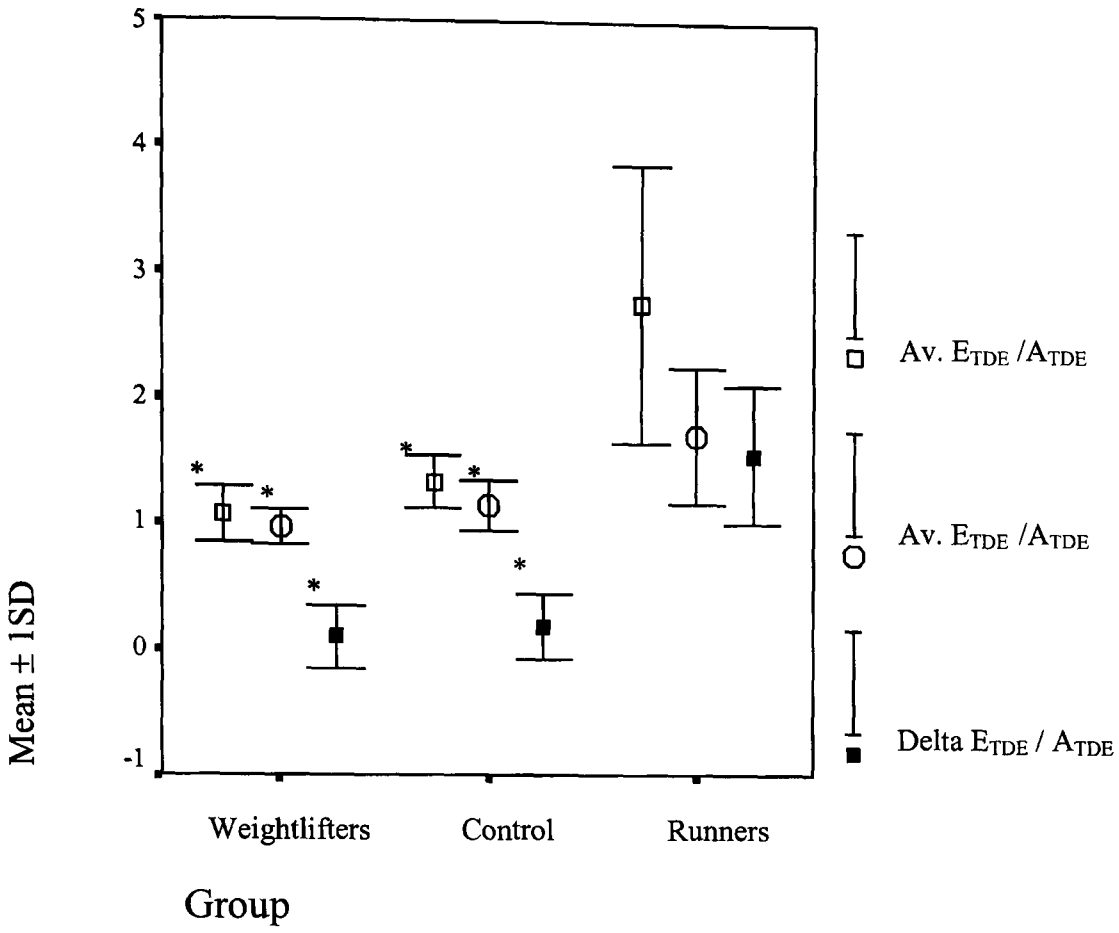

Figure 6.4 The ratio of E_{TDE} / A_{TDE} averaged across all four sites. * Denotes significantly different to runners.

Table 6.3 p - values for within group changes from baseline to post exercise.

	Runners	*Control*	*Weightlifters*
Av. Systolic Descent Pre - Post	**0.000**	**0.000**	**0.000**
Av. A_{TDE} Pre - Post	**0.000**	**0.000**	**0.000**
Av. E_{TDE} Pre - Post	**0.000**	**0.000**	**0.001**
Av. E_{TDE} / A_{TDE} Pre - Post	**0.002**	0.329	0.623
EDD Pre - Post	0.591	**0.010**	0.904
ESV Pre - Post	**0.003**	**0.000**	**0.021**

A_{TDE} = Annular velocity during atrial systole, E_{TDE} = annular velocity during early diastole, EDD = end diastolic volume, ESV = end systolic volume. Significant values are in bold.

Table 6.4 Short axis velocities at the posterior wall (PW) and interventricular septum (IVS) for each group.

	Weightlifter	*Controls*	*Runner*
IVS – SB	3.5 ± 1.6	2.91 ± 1.6	2.06 ± 0.9
IVS – EB	4.72 ± 1.3	5.58 ± 2.1	3.56 ± 1.1
IVS – AB	3.56 ± 1.9	2.47 ± 1.4	2.29 ± 0.8
IVS – EAB	1.72 ± 0.8	2.97 ± 2.1	1.92 ± 1.5
IVS – SE	7.36 ± 1.4*^	6.64 ± 1.9*	6.21 ± 2.5*
IVS – EE	6.38 ± 3.1*	7.69 ± 3.5*	7.09 ± 4.1*
IVS – AE	4.72 ± 2.4*	5.02 ± 1.5*	5.28 ± 4.1*
IVS - E / AE	1.56 ± 1.0	1.66 ± 1.0	1.70 ± 0.9
PW – SB	5.22 ± 2.1	6.35 ± 1.6	5.06 ± 0.9
PW – EB	9.18 ± 4.3	10.4 ± 2.1	11.5 ± 3.5
PW – AB	3.4 ± 1.2	4.0 ± 1.8	2.5 ± 1.2#
PW – EAB	3.19 ± 1.1	3.27 ± 1.1	3.92 ± 1.4
PW – SE	11.99 ± 3.1*	12.02 ± 2.5*	12.21±2.3*
PW – EE	11.3 ± 3.6	13.9 ± 3.5	12.9 ± 4.1
PW – AE	6.12 ± 3.3	8.39 ± 1.5	6.28 ± 4.1
PW – EAE	2.24 ± 0.8	2.33 ± 1.0	2.70 ± 0.9

SB = Systolic baseline, EB = E_{TDE} baseline, AB = A_{TDE} baseline, EAB = E_{TDE} / A_{TDE} baseline, SE = Systolic exercise, EE = E_{TDE} post exercise AE = A_{TDE} post exercise, E / AE = E_{TDE} / A_{TDE} post Exercise. ^ Denotes the percentage change from baseline to exercise is significantly different to controls. # denotes significantly different to controls, * denotes significant within group change from base to peak exercise.

6.4.3 GLOBAL DIASTOLIC FUNCTION

Resting global diastolic function was different between endurance trained and strength trained athletes. Although E wave velocity was not different between groups (83 ± 16 cm s^{-1} in runners *v* 84 ± 18 cm s^{-1} in weightlifters) the runners had a lower A wave velocity (53 ± 13 cm s^{-1} *v* 72 ± 11 cm s^{-1} $p < 0.001$), thus giving them an increased E / A ratio (1.62 ± 0.4 *v* 1.18 ± 0.23 $p < 0.01$). At rest E wave deceleration time, isovolumetric relaxation time and flow propagation velocity were not different between the two groups of athletes or the normal subjects. The E wave deceleration times were 119 ± 37 ms in runners, 174 ± 33ms in weightlifters and 176 ± 38 ms in control subjects. The mean isovolumetric relaxation times were 103 ± 18 ms, 78 ± 26 ms, and 84 ± 15 ms respectively. The average mitral inflow propagation velocities were 61 ± 12 cm s^{-1}, 61 ± 10 cm s^{-1} and 63 ± 15 cm s^{-1} respectively.

6.4.4 REGIONAL DIASTOLIC FUNCTION

Endurance trained athletes had augmented long axis function at rest compared with strength trained athletes (Table 3. Figure 2.). The mean E_{TDE} / A_{TDE} ratios at the four annular sites 2.22 ± 1.17 in runners, 1.09 ± 0.26 in weightlifters and 1.64 ± 0.54 in controls ($p < 0.01$). The only difference between the groups for short axis diastolic velocities at rest was a lower myocardial A_{TDE} wave in the left ventricular posterior wall in endurance trained athletes giving them a higher E_{TDE} / A_{TDE} ratio in this segment (table 6.4). Immediately after exercise diastolic early diastolic annular

velocities were similar between runners weightlifters and controls. However, the runners displayed lower A_{TDE} velocities both at rest and immediately after exercise although the relative change in A_{TDE} from rest to exercise was not different between groups. The runners also displayed higher E_{TDE} / A_{TDE} ratio both at rest and post exercise than either weightlifters or controls and the relative change in E_{TDE} / A_{TDE} ratio from rest to post exercise was also significantly greater. The runners were the only group whose E_{TDE} / A_{TDE} ratio post exercise was significantly different to their pre exercise ratio ($p < 0.01$).

6.4.5 Oxygen Consumption

Runners demonstrated higher $\dot{V}O_{2PEAK}$ than either weight trained or controls subjects, and thus had correspondingly higher exercise duration times and peak metabolic equivalents. The strongest univariate predictors of peak oxygen uptake ($\dot{V}O_{2PEAK}$) analyzed in all subjects together were: increase in HR from base line to peak exercise ($r = 0.63$, $p < 0.001$); from the M - mode echocardiographic data, resting end diastolic diameter index ($r = 0.57$ $p < 0.001$); from 2D cross sectional echocardiographic data end diastolic volume index immediately after exercise ($r = 0.47$ $p < 0.01$); from conventional Doppler mitral E / A inflow at rest ($r = 0.46$ $p < 0.01$); and from off line tissue Doppler indices of regional myocardial function the 4 - site averaged E_{TDE} / A_{TDE} ratio at rest ($r = 0.45$, $p < 0.01$). End systolic volume index at rest was a less strong predictor ($r = 0.39$, $p < 0.05$), left ventricular mass index was also a less strong

predictor ($r = 0.32$, $p < 0.05$). Whereas end systolic volume index immediately following exercise did not significantly correlate ($r = 0.26$, n.s.).

In order to find the combination of variables that best predicted exercise capacity, all variables both at rest and following exercise, and in addition blood pressure, systemic pulse pressure and cardiac index were entered into a multiple linear regression analysis. The best prediction of $\dot{V}O_{2PEAK}$ was obtained from a combination of resting end diastolic diameter, mitral E / A ratio, and immediate post exercise end diastolic volume index and averaged maximal early diastolic longitudinal velocity ($r = 0.74$, $r^2 = 0.55$, $F = 11.0$, $p < 0.001$). Since the morphological hypertrophy pattern in strength trained athletes is different (marked increases in wall size with no cavity enlargement), the linear regression analysis was repeated for the endurance trained athletes and normal subjects only. In this case only three variables predicted $\dot{V}O_{2PEAK}$ well, end diastolic diameter index at rest, end diastolic volume index immediately after exercise, and averaged maximal early diastolic longitudinal velocity after exercise ($r = 0.79$, $r^2 = 0.63$, $F = 14.8$, $p < 0.001$).

6.5 Discussion

This study has demonstrated that the endurance trained athletes had greater left ventricular long axis early diastolic filling velocities compared with strength trained athletes or normal controls

6.5.1 Strength Trained Versus Endurance Trained Athletes

At base line we found only minor structural differences between the two groups of athletes (table 6.1) and this is in agreement with a recent meta - analysis (Pluim & Zwinderman 2000). Global ejection fraction and regional systolic function measured from the velocities of myocardial segments were similar between all groups. However, endurance trained athletes had evidence of improved early diastolic filling compared to both other groups irrespective of whether this was assessed globally or regionally from long axis velocities.

6.5.2 Global Diastolic Function

Athletes heart is associated with normal or supernormal diastolic function at rest, and better diastolic performance than normal subjects during exercise (Finkelhor *et al.*, 1986; Stork *et al.*, 1992). The greater mitral E / A ratio seen at rest in endurance athletes was present without any increase in the absolute E wave velocity suggesting less dependence in trained hearts on atrial contribution to global diastolic filling at rest. This is due to a supranormal early diastolic relaxation (or ventricular suction). If true,

then endurance athletes would then demonstrate a greater increase in atrial phase filling on exercise. However, assessment of global diastolic function on exercise was limited due to fusion of the E and A wave velocities.

6.5.3 GLOBAL SYSTOLIC FUNCTION

This study demonstrated that endurance trained athletes increase their cardiac output on exercise through similar but more grater augmentation of their heart rate and ejection fraction than strength trained athletes. Immediately after exercise, ejection fraction was increased through a reduction of end systolic volume, whereas end diastolic volume was unchanged. These findings differ from previous findings in which end diastolic volume has increased by 14 % (Schairer *et al.*, 1992; Jensen - Urstadt *et al.*, 1998), although this may be due to the supine nature of the resting and post exercise examination in this study. Weightlifters had the highest mean LVM index, but on average their systolic myocardial velocities and peak exercise capacity was similar to controls.

6.5.4 LONG AXIS FUNCTION

There were also no significant differences between types of athletes in left ventricular long axis systolic velocities either at rest or immediately after exercise suggesting that neither endurance training nor weight training have any effect on long axis systolic function. Endurance trained athletes had better long axis diastolic function at rest than strength trained athletes. Runners demonstrated greater E_{TDE} at rest but not following

exercise, and a lower A_{TDE} at rest and following exercise. Furthermore, the mean difference in A_{TDE} between weightlifters or controls and runners was less following exercise thus the runners had a greater decrease in their E_{TDE} / A_{TDE} ratio from rest to post exercise suggesting greater atrial systolic reserve. Therefore, the effect of endurance training on cardiac adaptation is two fold. There are dimensional changes in both cavity size and wall thickness as mentioned previously, and there are functional changes in terms of relaxation velocities of the fibers of the long axis only. The changes in long axis relaxation velocity must be functional and not simply due to increased preload during exercise because; a) the difference in E_{TDE} was evident at rest and not post exercise when preload would have been greatest, and b) because previous work using rapid saline infusions of up to 2500 mL have failed to elicit changes in E_{TDE} (Alam *et al.*, 2000). The increased ventricular capacity, coupled with the higher relaxation rates serve to maximize ventricular volume at the end of early diastolic filling. This clearly suggests that endurance athletes are able to call on a greater atrial systolic functional reserve during exercise, presumably to aid cardiac output. Other investigators have suggested that endurance trained athletes can increase their stroke volume throughout incremental exercise (Gledhill *et al.*, 1994).

The runners A_{TDE} at peak exercise remained significantly lower than that of controls or weightlifters. Assuming that the runners are capable of the same A_{TDE} velocities as controls or weightlifters it is likely that this is due to the endurance athletes having a faster recovery. Thus runners were able to reduce their atrial contribution more

quickly after the exercise procedure than the other groups. However, the possibility of runners having a lower maximal A_{TDE} cannot be ruled out.

In this study both global and long axis diastolic velocities correlated with maximal oxygen uptake while short axis velocities did not. This suggests that the increased exercise capacity seen in runners may be partly explained by increased diastolic functional reserve. The factors that correlated with $\dot{V}O_{2PEAK}$ (E_{TDE} , resting EDD, mitral E, E / A at rest) may elucidate the mechanism for increased exercise capacity, at least in terms of central adaptation. At rest, the high E_{TDE} and high EDD maximize end early diastolic volume possibly enhanced by high E_{TDE} and high EDD generating greater ventricular suction. Furthermore, the high EDV means that resting O_2 demand can be mostly met by early diastolic filling alone and the atrial volume at end of early diastolic filling will be relatively low. The low atrial volume will generate a relatively low atrial systolic contraction due to a combination of low hormonal activation in basal states and low Frank Starling activation. Therefore, the high ventricular volume at the end of early diastole is itself the regulatory mechanism for atrial contraction. This in turn means there is a greater atrial reserve available during exercise. During exercise endurance athletes can increase their atrial systolic force as the increased preload will increase atrial volume at the end of early diastolic filling. It is important to differentiate this from reduced atrial filling fraction at rest seen in athletes. The lower mitral A wave (i.e. haemodynamic inflow across the mitral valve) seen in athletes is because ventricular pressure increases sufficiently to close the mitral leaflets after a relatively small atrial contribution. While there is undoubtedly some interplay

between ventricular pressure, atrial filling fraction and atrial systolic force, they are governed by separate regulatory mechanisms.

The reasons why changes in diastolic function appear to be confined to the long axis are probably related to its relatively poorer compliance compared to the short axis. In any healthy heart, long axis early diastolic lengthening begins commensurate with early diastolic inflow. However, long axis diastolic velocities (and therefore displacement) cease before early diastolic inflow, i.e. long axis early relaxation ends before early haemodynamic inflow (Gulati *et al.,* 1999). This by definition means that long axis compliance is maximal in a healthy heart at rest (Gulati *et al.,* 1999). Therefore the greatest training effect is likely to be on the fibers of the long axis as these reach their maximal functional diastolic capacity before other fibers of the ventricular wall. Cavity enlargement occurring primarily across the chamber short axis may compound this, as the fibers of the short axis reach their maximal compliance at higher volumes, and thus do not have the same diastolic stress that is seen in the fibers of the long axis. So during endurance training, with extended periods of increased preload, the long axis will experience the greatest stress.

During exercise stress the beta - adrenergic stimulation of the ventricular myocytes produces reductions in myofilament Ca^{2+} sensitivity, increases the rate of actin myosin cross bridge turn over and accelerate the sequestering of Ca^{2+} into the sarcoplasmic reticulum (Walsh 1990). All these sub - cellular mechanisms result in an increased rate and extent of ventricular relaxation (Walsh 1990). Furthermore they are thought

to be due beta adrenergic mediated phosphorylation of phospholamban, troponin I and c - protein (Kaumann 1999).

It is proposed from this data that the endurance exercise mediates its effects on cardiac adaptation via increased myocardial adrenergic sensitivity at rest compared to either controls or weightlifters. The improvements in endurance athletes diastolic function were due to faster relaxation velocities at rest. Furthermore, the E_{TDE} velocities were not different between groups at peak exercise and runners A_{TDE} velocities were lower than either the control group or the weightlifters. Correspondingly, the greater change in E_{TDE} / A_{TDE} ratio demonstrated by the endurance trained athletes was due to greater early diastolic lusitropic activation at rest. This means that endurance training does not increase the maximal relaxation rate of myocytes in the fibers of either the long or short axis. It is unlikely therefore that improvements in diastolic function are due to increases in the intracellular concentration of the molecular determinants of Ca^{2+} clearance ($SRCa^{2+}$ ATPase, calsequstrin, phospholamban) as this would create an increase in both the basal and peak relaxation velocities. However, the data here is consistent with increased lusitropic sensitivity to beta - adrenergic stimulation at rest in endurance trained athletes. This would explain the improved diastolic function at rest without improvements at peak exercise. Investigations of the effect of endurance training on these regulatory proteins have demonstrated little or no change in their intra cellular concentrations (Arai *et al.*,1995.) and endurance training is associated with unchanged or reduced resting plasma catecholamine levels (Romijn *et al.*, 1995). Previous work on endurance training and catecholamine sensitivity has focused on

systolic performance. Spina *et al.*, (1998) demonstrated that endurance trained older individuals demonstrate increased systolic sensitivity to beta adrenergic stimulation, and regular exercise has been shown to increase the sensitivity of coronary vascular beds to beta adrenergic stimulation (DiCarlo *et al.*, 1989). Increased numbers of beta 2 receptors on intact leukocytes from trained individuals have also been demonstrated (Lehman *et al.*, 1984). However, more work on human ventricular receptors with specific reference to diastolic activation is required.

Finally, the data here agree with Alam *et al.*, (2000) who suggest that E_{TDE} / A_{TDE} ratio is unaffected by heart rate in normal subjects. In fact this can be extended to subjects not involved in endurance exercise, as the weightlifters also demonstrated no significant change from rest to exercise. Alam *et al.*, (2000) demonstrated no differences in long axis diastolic velocities in response to changes in heart rate. In this study however, there were significant increases in peak E_{TDE} and A_{TDE} in response to the exercise mediated increase in heart rate. The difference seen in this study is probably due to the greater increase in heart rate as opposed to increases of 10 bpm induced by Alam *et al.*, (2000).

6.5.5 SHORT AXIS FUNCTION

There were few differences between the runners weightlifters or the controls in either systolic or diastolic short axis velocities whether measured at rest or post exercise. The only major difference with respect to the short axis was in terms of chamber dimensions. The runners had greater diameters across the short axis (measured by

EDD) than the controls. Therefore the major adaptation to chronic endurance exercise appears to differ for each axis. The major effect on the long axis is functional while the major effect on the short axis is primarily morphological. However, as the majority of the musculature of the ventricular walls is responsible for short axis movements (~ 95 % Jones *et al.,* 1990), and as force is proportional to mass (F = ma) the increase ventricular mass seen in endurance training will increase systolic force for the same contraction velocity. For the same reason, the greater mass of relaxing muscle of the short axis may also aid ventricular suction. Therefore although the primary adaptation of the short axis may be morphological, these changes have important functional consequences.

This identifies significant differences in how the long and the short axis contribute to global cardiac pump function. The short axis has greater mass and lower velocities while the long axis has much less mass but faster systolic and diastolic velocities. This is the mechanism by which the contribution of the long axis to systolic function is greater than may be expected by the contributing mass of muscle. In terms of efficient cardiac adaptation to endurance exercise it is clear that the increase in wall thickness seen by runners has a dual purpose. What is less clear is whether increased wall thickness, by default increases the mass of the sub endocardial layer, or whether the increase in mass is axis specific. As there is little change in long axis length in response to endurance training (Pluim and Zwinderman 200), it is possible that due to the law of LaPlace there may be no remodeling in this myocardial layer. However, there are no currently available data to support or reject this hypothesis.

6.5.6 EXERCISE CAPACITY

The volunteers recruited for this study were club athletes rather than elite athletes, but changes were seen. Resting EDV and LVM were similar to those reported previously (Pluim & Zwinderman 2000). These subjects therefore constituted a suitable population in which to test for correlations between haemodynamic parameters and $\dot{V}O_{2PEAK}$ (the range of $\dot{V}O_{2PEAK}$ was 21.9 to 60.3 ml Kg^{-1} min^{-1}).

The major cardiac determinants of $\dot{V}O_{2PEAK}$ observed in this study were all related to diastolic loading or early diastolic filling. Increases in early diastolic lengthening velocity of the long axis of the left ventricle (E_{TDE}) correlated with $\dot{V}O_{2PEAK}$ implying that ventricular suction may be augmented in endurance - trained athletes.

In experimental studies on animals maximum cardiac output is limited by the development of pericardial constraint during exercise (Hammond *et al.*, 1992). In addition end diastolic volume and cardiac output at peak exercise are increased following pericardectomy (Hammond *et al.*, 1992; Stray - Gunderson 1986). Our data in man are consistent with this hypothesis in that endurance trained but not strength - trained athletes augment cardiac performance by increasing early diastolic filling and through chronic adaptive enlargement of the pericardial cavity in response to repeated volume overload during training. Resting systolic myocardial velocities were similar between the athletes and the normal subjects, but the endurance trained athletes had a better exercise capacity, which correlated with increased EDV and E_{TDE} / A_{TDE} thereby confirming the hypothesis. While strength trained athletes in this study displayed the

greatest mean LVM index this adaptive hypertrophy caused by isometric exercise did not translate into better exercise capacity compared with normal subjects. However, whether the weightlifters would demonstrate functional changes compared to normals in the face of acute increases in afterload is unknown.

Previous studies have addressed the relationship between diastolic function and exercise capacity, but they did not employ methods that were able to characterize regional myocardial function in detail or immediately after exercise. Levy and co workers (1993) utilized radionuclide methods during supine bicycle exercise and Vanovershelde *et al.,* (1993) compared $\dot{V}O_{2PEAK}$ during upright cycle exercise. Using multiple linear regression analyses both these studies identified peak mitral filling rate, mitral E / A ratio as well as end systolic volume at rest as predictors of $\dot{V}O_{2PEAK}$. Vanoverschelede *et al.,* (1993) also determined that after endurance training mitral A velocity decreased. This study found reduced mitral A wave at rest in endurance trained athletes. This is indicative of improved early diastolic filling rather than a mild restrictive pattern. This study extends the observations of these previous reports by demonstrating the predominant effects of endurance training in terms of myocardial velocities on longitudinal diastolic function, and by identifying that regional diastolic function during exercise is also a significant predictor of $\dot{V}O_{2PEAK}$.

6.5.7 STUDY LIMITATIONS

Three of the weightlifters admitted to taking anabolic steroids. The use of anabolic steroids during physical training probably exacerbates the development of LVH, but effects on diastolic function have not been proven (DePiccolo *et al.*, 1991; Dickerman *et al.*, 1998; Thompson *et al.*, 1992; Yeater *et al.*, 1996). In our study none of the weightlifters taking anabolic steroids had diastolic dysfunction defined as E / A ratio < 1 and or E_{TDE} / A_{TDE} ratio < 1 and thus were not excluded.

It is not possible to perform detailed echocardiographic examination of regional myocardial function during upright exercise. Treadmill exercise was chosen for this study because it provides the most normal physical stress, leading to the unavoidable compromise of measuring cardiac function immediately after exercise. Acquisition of data was limited to those recordings that could be made within 2 minutes of the end of exercise and in each subject recordings were obtained in the same sequence. (apical before parasternal views). The storage of digital loops containing full echocardiographic data allowed for detailed examination by subsequent post processing.

Immediately after exercise (i.e. within one minute), there are substantial and significant reductions from peak values in heart rate, systolic blood pressure and cardiac output (Flam *et al.*, 1990). There is an acute but transient increase in ejection fraction due predominately to a sudden decrease in end - diastolic volume, caused by an immediate fall in venous return as the effect of the skeletal muscle pump is lost and

splanchnic vasoconstriction is reversed. At two minutes haemodynamic loading and performance remain significantly different to baseline (Flam *et al.,* 1990) thus the measurements that we obtained will have underestimated peak changes. Nevertheless our measured "peak" cardiac index was on average 14 L min^{-1} m^{-2} in runners who reached a $\dot{V}O_{2PEAK}$ of 50 ml Kg^{-1} min^{-1} .

6.6 CONCLUSION

Endurance trained athletes demonstrated changes in cardiac morphology and function aimed at maximizing early diastolic filling compared with strength trained athletes or controls. These changes were evident at rest rather than at peak exercise and correspondingly resulted in a greater functional reserve during exercise, specifically in left atrial systolic function. These changes may be related to greater sensitivity of endurance trained hearts to beta adrenergic stimulation. Furthermore, the changes in long axis diastolic function were significant correlates of $\dot{V}O_{2PEAK}$. Left ventricular long axis systolic function however, appeared unchanged by either method of training. The effect of training on the short axis appears to be mostly morphological although this in turn will have functional consequences. Endurance athletes also had higher chronotropic and global systolic functional reserve. These changes are responsible for the better exercise capacity of the endurance - trained athletes.

CHAPTER 7: SUMMARY OF FINDINGS AND DIRECTIONS FOR FUTURE DEVELOPMENT

7.1 CONFIRMATION OF REJECTION OF HYPOTHESES

The results of study one indicate that all parts of both H 1 and H 2 (see p 71) should be rejected. Both the endurance trained group (H 1) and the resistance trained group (H 2) demonstrated significantly faster systolic, E_{TDE} and A_{TDE} long axis function than patients with pathological left ventricular hypertrophy. Similarly, the long axis function of senior endurance athletes (H 3) and resistance athletes (H 4) was also significantly different to that of the older patients with pathological LVH and hence all parts of these hypotheses are also rejected. The hypotheses that long - term endurance training (H 5) or resistance training (H 6) would not prevent the age related decline in long axis function are also rejected on the evidence of study 3. Study 4 demonstrated that there was no difference in the long axis systolic or E_{TDE} long axis function between endurance athletes and controls. So H 7 A and B are accepted, however A_{TDE} was significantly lower in the runners than in the controls and hence H 7 C is rejected. All parts of H 8 are accepted, as the weightlifters demonstrated no difference in long axis function compared to controls in either systolic, E_{TDE} or A_{TDE} longitudinal velocities. H 9 is accepted as neither systolic, E_{TDE} or A_{TDE} velocities correlated significantly with peak exercise capacity, however resting E_{TDE} / A_{TDE} ratio was significantly correlated $\dot{V}O_{2PEAK}$ indicating that diastolic changes are implicated in the ability of endurance athletes to achieve higher peak rates of O_2 consumption.

7.2 MAJOR FINDINGS

The results of both studies 1 and 2 demonstrated that measurement of longitudinal function is useful in the evaluation and differentiation of pathological and physiological left ventricular hypertrophy. Both systolic and E_{TDE} long axis velocities differentiated well between pathological and physiological hypertrophy. In addition the ability to discriminate between groups was possible even in older subjects. Long axis analysis may also aid in differentiating different types of pathological hypertrophy as demonstrated in study 2 were the heterogeneity index of the systolic descent around the mitral annulus did differentiate between LVH due to hypertrophic cardiomyopathy and hypertension. Comparisons of studies 1 and 2 confirmed previous reports of age related declines in longitudinal function (Onose *et al.*, 1999; Alam *et al.*, 1999; Yamada *et al.*, 1999). However, contrary to previous reports we found that increases in heart rate resulted in significant changes in long axis function. Furthermore, it was demonstrated that both endurance and resistance type exercise can attenuate the age related decline in systolic function. It was also evident that in terms of pathology there was no further increment in the decrease in either systolic or diastolic velocities when pathology and age were combined. While this may be an indication that the same mechanism may be responsible for the two types of functional decrease, the wide inter - individual variation in response to HCM and HT make interpretation of age related changes difficult.

Study four demonstrated that one of the mechanisms of cardiac adaptation in endurance athletes is superior diastolic longitudinal function. This was evident at rest, which may be evidence of increased sensitivity to sympathetic activation. The increased early diastolic filling in endurance athletes resulted in less atrial contribution at rest and a correspondingly higher atrial systolic reserve available during exercise. Furthermore, in study four, systolic velocities were not different between any of the groups, either at rest or peak exercise demonstrating that exercise training of either type does not affect systolic long axis function. Therefore it is possible that systolic long axis velocities may be useful in identifying pathological LVH in athletes because exercise induced increases in function will not mask pathologically induced decreases in function. Additionally in study 1 the ability of systolic or diastolic descent velocities to differentiate between HCM and physiological LVH was highly sensitive, and as most cases of sudden death in athletes under 35 are due to undiagnosed cardiomyopathy then such a test would have obvious implications for athlete screening.

7.2 Future Directions

Although the ability of long axis function to identify pathology in athletes is speculative, a prospective study of athletic populations is warranted in order to determine the efficacy of such a test. Furthermore the evaluation of long axis velocity in athletes with known hypertrophic cardiomyopathy would also be of interest. It is

also important to extend the range of these findings and evaluate the proposed test in females and in other types of cardiomyopathy.

Elucidation of the mechanisms of effect of endurance exercise on diastolic function is another avenue for investigation. It is currently unknown whether short axis dilation and increased diastolic long axis velocity occur together, or whether increased diastolic velocity allows for greater early diastolic filling, which in turn causes the chamber dilation, alternatively chamber dilation may be the primary stimulus and long axis diastolic velocities may increase order to keep pace with the short axis morphological changes. Furthermore the time course for changes in diastolic long axis function needs to be evaluated. How long is necessary for changes to become evident, whether they are related to training volume or intensity or both needs to be evaluated. The application of these criteria to cardiac patients with diastolic dysfunction may be of specific value.

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APPENDIX 1 SUBJECT INFORMATION & CONSENT SHEET

Can assessment of long-axis function diffrentiate between pathological and physiological left ventricular hypertrophy?

Information for Volunteers.

As you probably know, an athletes heart may be different from the heart of a sedentary person. Because of training the mass of the heart nay increase. This type of thickening or hypertrophy of the heart is called physiological because it seems to not carry any risk for health. However, some athletes may have a disease of the heart which is also associated with muscular hypertrophy. Differentiation of these 2 types of hypertrophy is difficult, but a new type of echocardiography may allow us to develop a simple test that can distinguish between pathological and physiological hypertrophy. But in order to do this we need normal healthy volunteers, as well as athletes and individuals with pathological heart conditions.

This study involves an ultrasound examination of your heart at rest. This is a special form of echocardiogram where we look at the movements of the walls of the heart, measuring the velocities of every wall using some new software. This will take about 40 minutes. It is the same sort of technology used to look at babies in the womb and will not hurt in any way.

We would also like you to exercise, but to do this safely we will take some clinical details and examine you. We would also like to take a small blood sample to measure your blood fats, blood count and kidney function. We would like to freeze a small portion of your blood to measure substances that may be responsible for controlling heart growth. You will be asked to fill in a short questionnaire to gauge the amount of exercise you take on a regular basis. This information is confidential and will not be sent to your GP without your consent.

We would like you to exercise on a treadmill, for as long as you can without being ill. Your cardiograph and blood pressure will be measured every 3 minutes to ensure our safety. Every 3 minutes the treadmill will get faster and harder and during the exercise we will ask you to breath through a mouthpiece so that we can measure your ability to use oxygen and so asses your fitness. This is a standard way of looking to see how fit you are and is used in association with a measure of lactate in you blood using a sample taken from your ear lobe. Immediately after the exercise we would like to repeat the echocardiogram.

We would be grateful if you could consent to take part in this study. If you volunteer you can still withdraw from this study at any time should you wish to. If you require any further information, please ask. Or you can speak to any of the people listed below. At the end of the study you will be sent a report of your fitness level if you leave us your address.

Dr Alan Fraser	Dr Anne Tweddle	Dr Dragos Vinereanu	Nick Sculthorpe
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